Hepatitis among Greenlanders in Denmark and in Greenland, and the outcome of chronic HBV-infection in Greenland

Rex, Karsten Fleischer

Publication date:
2019

Document Version
Publisher's PDF, also known as Version of record

HEPATITIS AMONG GREENLANDERS IN DENMARK AND IN GREENLAND, AND THE OUTCOME OF CHRONIC HBV-INFECTION IN GREENLAND

BY
KARSTEN FLEISCHER REX

DISSERTATION SUBMITTED 2019

AALBORG UNIVERSITY
DENMARK

HEPATITIS AMONG GREENLANDERS IN DENMARK AND IN GREENLAND, AND THE OUTCOME OF CHRONIC HBV-INFECTION IN GREENLAND

by

Karsten Fleischer Rex

AALBORG UNIVERSITY
DENMARK

Dissertation submitted September 12th 2019

Dissertation submitted:	September 12th 2019
PhD main supervisor:	Stig Andersen, MD, PhD, Professor, Head, Arctic Health Research Centre, Department of Clinical Medicine, Aalborg University Hospital, Denmark & Professor, University of Greenland
PhD co-supervisor:	Henrik Krarup, MD, PhD, Head, Department of Molecular Diagnostics, Aalborg University Hospital, Denmark
Assistant PhD supervisor:	Michael Lynge Pedersen, MD, PhD, Dr. Med. Sci., District Medical Officer, Dronning Ingrids Sundhedscenter, Nuuk, Greenland & Associate Professor, University of Greenland
PhD committee:	Anne Merrild Hansen, Professor Aalborg University
	Gerda Elisabeth Villadsen, Associate Professor, MD Aarhus University
	Prabhu P. Gounder, MD, MPH, FACP, Medical Director Los Angeles Department of Public Health
PhD Series:	Faculty of Medicine, Aalborg University
Department:	Department of Clinical Medicine

ISSN (online): 2246-1302
ISBN (online): 978-87-7210-471-3

Published by:
Aalborg University Press
Langagervej 2
DK – 9220 Aalborg Ø
Phone: +45 99407140
aauf@forlag.aau.dk
forlag.aau.dk

Printed in Denmark by Rosendahls, 2019

AUTHOR INTRODUCTION

Karsten Fleischer Rex, born 1979, Maniitsoq, Greenland. Master in Medicine 2009 from Aarhus University, Denmark. Completed a 5-year specialist training in Greenland in General Medicine by 2017. Staff specialist at the Department of Internal Medicine, Queen Ingrid's Hospital, Nuuk, Greenland 2017. Part time Ph.D. student 2014-2019 from the University of Aalborg and the University of Greenland on chronic hepatitis B infection among Greenlanders.

The PhD included HBV data-collection on Greenlanders in Denmark and a 10-year follow-up data collection on a 1998 Greenlandic cohort in Greenland using all available registries and electronic medical records. In addition, I have engaged in a number of activities in relation to science in the Arctic. These include a presentation on hepatitis B, D and C on Greenlandic Inuit migrated to Denmark at the 15th International Congress on Circumpolar Health (ICCH15)**.** Speaker at the NunaMed 2013 Conference on "HBV and Alcohol" and "weight among children in Greenland at school-entry" in Nuuk, Greenland. Speaker on "HBV in Greenland" at the "World Indigenous Peoples' Conference on Viral Hepatitis" in Australia in 2014. Speak at the Greenland Medical Society, Copenhagen Denmark meeting on "Chronic hepatitis B and monitoring in Greenland" in 2014 in Copenhagen, Denmark and attended

meeting in 2015. Speaker on 'Hepatitis' at the Medical staff forum, DIH, Nuuk 2016 and speaker on 'Ethical Principles in HBV research' at the PhD summer school in Nuuk in 2016. Chairman and speaker on the 'HAV, HBV and the HDV'-session on 'the HBV and HDV-outbreak in Itilleq Greenland on a clinical view, containment and vaccination strategies', at NunaMed 2016. Teaching staff at the Sisimiut Health Care Centre, Greenland 2017 and staff at the Internal Medical Department Nuuk 2018 on Hepatitis B diagnostics and occult hepatitis B infections. Global Health Course Speaker on 'Hepatitis B & D' and 'working as a M.D. in Greenland', August 30th, Nuuk Greenland 2017. Also, teaching staff at Queen Ingrid's Health Care Centre (DIS Nuuk) on HBV and overall survival based on PhD study findings 2018. Presenting PhD findings on HBV and overall survival June 2018 at PhD course in Nuuk and later presenting findings at the ICCH17 also being ICCH Chairman on the 'HIV, HPV and viral hepatitis' session. Furthermore, keynote speaker on 'Being indigenous and returning to serve a native population' at the ICCH17. In addition, it was an honor to receive the Jens Peder Hart Hansen Award at the ICCH in 2015.

HBV related activities have been an integral part of my clinical work. This include updating the Clinical Guideline for HBV vaccination among newborns in DIH Nuuk, treatment and blood sampling guidelines for pregnant and adult patients in Greenland on HIV, HBV and HDV infections. Visiting hyper-endemic HBV and HDV village Itilleq in Greenland for blood sampling, vaccination, management, treatment and future monitoring capabilities on August 19-20th, 2015 and September 21st, 2016. Monitoring of HBV and HDV in a local municipality "Qeqqa Kommunia" in Sisimiut Greenland and surrounding villages by paraclinical assessment, 2016-17. Working in the weekly infectious disease outpatient clinic concerning tuberculosis, HIV and hepatitis at Queen Ingrids Hospital, Internal Medical Department, Nuuk from 2017. Being a consultant at the Internal Medical Department in Nuuk concerning hepatitis- and HIV-related questions among others from all of Greenland.

Queen Ingrid's Hospital Nuuk

Itilleq settlement in Greenland

ABSTRACT (SUMMARY IN ENGLISH)

Background

HBV-infection is a global health problem and may cause end-stage liver disease including liver cirrhosis and hepatocellular carcinoma (HCC). Due to the poor prognosis, HCC is the third most common cause of cancer related death. HBV-infection is known to be endemic among the arctic Inuit and in regions of Greenland prevalence of HBV has been found to be as high as 29%. The overall low incidence of HCC in chronically HBV-infected Greenlanders has suggested a more benign course of infection in Greenland than in other parts of the world.

Aim

The overall aim of this PhD study was to elucidate disease burden of HBV-infections in the Greenlandic population. This assessed by comparing Greenlanders with frequent HBV-infections to migrated Inuit Greenlanders in a subsequent cross-sectional study in Denmark in 2006. In addition, assessing overall survival and disease burden over a course of ten years. Secondarily, we wanted to cultivate a foundation for a future monitoring program and containment of HBV-infections in Greenland.

Methods

We performed an interview on dietary habits, smoking habits and on alcohol use through two population-based studies. Clinical assessment on body build parameters, blood sampling on liver function tests and markers of HBV-infection was investigated. All available registers and electronic medical records were reviewed for a HBV-related 10-year follow up on participants in Greenland. Secondarily, working in different parts of Greenland with hepatitis patients during the course of the 5-year

part time PhD made a foundation on an idea for a future monitoring program and containment of HBV-infections in Greenland.

Results

A total of 671 Greenlanders in Greenland and Inuit in Denmark were surveyed. Prevalences of serological markers of hepatitis B, D and C virus infection showed no difference between Greenlanders living in Greenland and Greenlanders migrated to Denmark. Our studies did not show evidence of serological or clinical signs of disease when comparing HBV-infected to non-infected.

Inuit had lower alcohol use. In general, Greenland Inuit had higher levels of AST, GGT and ALK than non-Inuit. The association between AST and alcohol intake was modified by ethnic origin with higher levels of AST among Inuit than on non-Inuit on the increase of alcohol use.

In contrast to Greenland intravenous drug use can occur in Denmark. This may introduce a new way of transmission of disease among Greenlanders.

Survival analyses show a markedly decrease in lifespan among the infected on a 10-year period of follow-up.

Conclusion

We document that HBV-, HDV- and HCV-infection marker proportions in Denmark Inuit mirror proportions reported in Greenland. This imply infection on Greenland Inuit before migration on an earlier age from a high endemic area to a low endemic area. We find evidence of the possibility of HBV-infections to be transmitted in adulthood in addition to infection transmission earlier in life in Greenland. Intravenous drug use has been considered non-existing among Inuit in Greenland.

Our study show that intravenous drug use can be introduced to Greenlanders on migration and the possibility of infection by this route therefore exists in the studied population. We suggest ethnic differences in liver biochemistry. There was no evidence of a HBV-related disease judging on clinical manifestation or on LFTs. The profound reduced lifespan among the HBV-infected could not be directly ascertained to severe HBV-related diseases when looking into data registries and EMRs. We consider that HBV-infection in the Greenland Inuit population may not be the benign disease that has been previously suggested.

Public health implications

In a clinical setting, matters on HBV-infections have lost their momentum in Greenland with the risk of undiagnosed HBV-related deaths. HBsAg-positivity in the population still occur. The development in Greenland in general leaves great enhancement opportunities for HBV-monitoring. A feasible way of getting a clinical database on HBV-infected and HBV-exposed in Greenland is to gather all available data on infection status found in clinical and in research settings. Management should also rely on diagnosis by a yearly extraction of HBV-serology from the nationwide laboratory findings. Monitoring HBV-infections in Greenland will in turn give a better understanding of the disease, to insure treatment on indication and to reduce the risk of cirrhosis, end stage liver disease and HCC. HBV-vaccines to all non-exposed Greenlanders and to immigrants will be an effective way to lessen HBV-related problems in the future.

DANSK RESUMÉ (SUMMARY IN DANISH)

Baggrund

Hepatitis B-infektion (HBV-infektion) er et globalt sundhedsproblem, som kan føre til følgesygdomme som skrumpelever og hepatocellulært karcinom (HCC). Grundet dårlig prognose er leverkræft (hepatocellulært karcinom [HCC]) den tredje mest almindelige årsag til kræft-relateret død. HBV-infektioner er endemiske i Inuitbefolkninger i Arktis og i områder i Grønland er prævalencen fundet så høj som 29%. Grundet den lave forekomst af HCC blandt kronisk inficerede Hepatitis B bærer i Grønland har man formodet et mere benignt forløb her end i andre steder i verden.

Formål

Det overordnede mål for denne PhD-afhandling er at belyse sygdomsbyrden ved HBV-infektion i den grønlandsk befolkning. Dette vurderet ved at sammenligne grønlændere med hyppig forekomst af HBV-infektioner i Grønland med grønlændere i Danmark. Derudover at vurdere overlevelse og sygdomsbyrde over en tiårs periode. Sekundært at kultivere et fundament for et muligt monitoreringsprogram og inddæmning af HBV-infektioner i Grønland.

Metoder

Gennem to populationsbaserede studier blev der udført et interview med fokus på kostvaner, rygevaner og alkoholforbrug. Mål for kropsbygning og blodprøver med undersøgelse af levertal og HBV-infektionsmarkører blev udført. Alle disponible registre og elektroniske patient journaler blev gennemgået med henblik på en HBV-relateret tiårs opfølgning på deltagere i Grønland. Et grundlag for udarbejdning af et muligt fremtidigt program for monitorering og inddæmning af leverbetændelse i

Grønland baseredes på arbejde i Grønland med blandt andet leverbetændelsespatienter i perioden for den 5-årige deltids-PhD-ansættelse.

Resultater

I alt blev 671 grønlændere i Grønland og Inuit i Danmark undersøgt. Prævalencerne af serologiske markører for leverbetændelse type B, D og C var uden forskelle mellem grønlændere i Grønland og grønlændere som var immigreret til Danmark. Vores studie viste heller ingen evidens for forskelle i levertal eller kliniske tegn til sygdom når man sammenlignede HBV-smittede med ikke-smittede.

Inuit havde lavere alkoholforbrug. Inuit havde generelt højere værdier af AST, GGT og ALK end ikke-Inuit. Associationen mellem AST og alkoholindtagelse modificeredes af etnisk baggrund med højere værdier af AST hos Inuit end ikke-Inuit ved øget alkoholforbrug.

I modsætning til i Grønland kan intravenøs stofmisbrug forekomme i Danmark. Dette kan introducere en ny måde for mulig smittespredning blandt grønlændere. Overlevelsesanalyserne viser en markant nedsat levetid for de HBV-inficerede i forhold til ikke-inficerede over en 10-års periode.

Konklusion

Vi dokumenterer at proportionerne på HBV-, HDV- og HCV-infektionsmarkører blandt grønlændere i Danmark ligner proportionerne i Grønland. Dette formås at kunne skyldes infektion før immigration fra et høj-endemisk HBV-område til et lav-endemisk område. Vi finder evidens for at HBV-smitte i Grønland kan forekomme i voksenalderen ud over smitte tidligere i livet. Intravenøs stofmisbrug er vurderet som ikkeeksisterende blandt Inuit i Grønland.

Vores undersøgelse viser at intravenøs stofmisbrug kan blive introduceret til den grønlandske befolkning ved migration og der foreligger herved en ny måde hvorpå smittespredning kan foregå.

Vi antyder at der kan foreligge forskelle i leverbiokemi på baggrund af etnicitet. Der var ingen evidens for HBV-relateret sygdom vurderet ud fra kliniske manifestationer og levertal.

Den markant reducerede levetid for de HBV-inficerede kunne ikke direkte relateres til HBV-følgesygdomme når man så på dataregistre og elektroniske patientjournaler. Vi overvejer dog at HBV-infektion i Grønland måske ikke er den benigne sygdom, som før antaget.

Folkesundhedsmæssige implikationer

I den kliniske hverdag har HBV-infektioner tabt fokus i Grønland med risiko for underdiagnosticerede HBV-relaterede dødsfald. HBV-smitte forekommer fortsat. Udviklingen generelt i Grønland giver gode muligheder for forbedringer i HBV-monitorering. En mulighed for at få en database over HBV-inficerede og HBV-eksponerede i Grønland vil være at indsamle al tilgængelig data på HBV-målinger blandt grønlændere foretaget i den kliniske hverdag samt fra forskningssammenhænge. Registrering og styring bør også bygge på diagnose ved udtræk af HBV-serologi fra det landsdækkende laboratorie-register. Monitorering af HBV-infektioner i Grønland vil give bedre forståelse for sygdommen og forsikre behandling på indikation samt reducere risikoen for følgesygdomme heraf.

HBV-vaccine til alle ueksponerede grønlændere og immigranter vil være en effektiv måde hvorpå HBV-relaterede problemer kan mindskes i fremtiden.

Kalaallisut eqikkarneqarnera (Summary in Greenlandic)

Tunuliaqut

Tunillannartumik tingukkut aseruuttoorneq type B (HBV) nunarsuatsinni nappaatit kingunerisinnaasai ukuusinnaasut pillugit peqqinnissamut aarlerinarsinnaavoq; tinguup eqinnera imaluunniit tingukkut kræfteqalertarneq (HCC). Tingukkut kræfteqarneq (HCC) ajorunnaarsaruminnaannera pillugu kræftimik toqussutaasartoq pingajorivaat. Innuttaasuni nunani issittuni Kalaallit Nunatsinnilu najugalinni annerpaamik 29%-iisa tuniluuttumik tingulluummik type B (HBV) tunillatsinnikuupput. Kalaallit Nunatsinni tingullunnermik ataavartumik type B-mik tunillatinnikut akornanni tingumikkut kræfteqalersartut (HCC) naammattuugassaavallaanngillat. Tamatumunnga pissutaasorineqarpoq tingullulersimasut oqinnerusumik atugassaqarsimanerat.

Siunertaq

Ilisimatuutut allaatigisami pingaarnertut siunertaavoq kalaallini Kalaallit Nunaanni najugaqartuni aammalu kalaallini Danmarkimi najugaqartuni tingullunnerup atugaanera erseqqissassallugu.

Misissuinermi tunngaviusut ilagaat Kalaallit Nunatsinni tingullunnermik tunillatinnikut nakkutilliiveqalernissaat.

Periaaseq

Misissuinerni marluusuni peqataasut apersorneqarneranni nerisaqarneq, tujortarneq imigassartortarnerlu qitiutinneqarput. Peqataasut timip sananeqaataanik misissorneqarput tingullunnermullu aaversinnermi misissorneqarlutik. Ukiut qulit qaangiunnerini peqataasut Kalaallit Nunatsinni

najugaqartut malittarineqarsinnaaniassammata peqqissutsikkut nalunaarsorsimaffiit tamavimmik misissorneqarput.

Ukiut tallimat ingerlaneranni ilisimatuutut ilinniarnermi (PhD) siunertarineqarpoq Kalaallit Nunatsinni tingukkut aseruuttoornermi nakkutilliiveqalernissaq aammalu tunillaassuineq annikillisinneqarnissaa.

Kingunerisat

Kalaallit katillugit 671-it Kalaallit Nunatsinni Danmarkimilu najugallit misissuinitsinni peqataapput.

Peqataasut tuniluuttumik tingulluummik tunillatsinnikut tunillatsinneqanngittullu timimikkut misissortinneri aaversinnerisalu inerneri sanilliutissagaanni assigiipput.

Kalaallit qallunaanut sanilliullugit imigassamik atuinerat annikinnerugaluartoq aaversinnerini tinguup kisitsisai qullasinnerupput.

Taqarorluni ikiaroornartutalimmik kapoortarneq Danmarkimi atugaasinnaavoq. Kalaallit Danmarkimi najugallit taqarorlugu ikiaroornatutalimmik kapoortartut ikikkaluartut tuniluuttumik tingullunnermik tunillaasuusisinnaanerat peqqutaasinnavoq.

Misissueqqissaarnerup takutippaa ukiut qulit ingerlaneranni tuniluuttumik tingulluummik type B-mik tunillatsissimasut tunillatsissimanngitsuniit sanilliullugit sivikinnerusumik inuuneqartut.

Inerniliineq

Uppernarsarparput aaversinnerni tingullunnerup suussusaanik misissuinermi (HBV, HDV aamma HCV) kalaallit Danmarkimi najugalinni kalaallillu Kalaallit Nunatsinni najugalinni assigiittut.

Tassunga peqqutaasorivarput inuit nutsinnginnerminni tuniluuttumik tingulluummik tunillatsissimanerat. Misissuinitsinni aamma uppernarsarparput inersimasunngornermi tingulluummik tunillatsittoqarsinnaammat. Kalaallit Nunaanni taqarorluni ikiaroornatutalimmik kapoorineq atugaanngilaq. Misissuinitta takutippaa kalaallit Kalallit Nunaata avataannut nutsernikut taqarorlutik ikiaroornartutalimmik kapoorinermik atuisalersinnaanerat. Taannalu pillugu tuniluuttumik tingulluummik tunillatsissinnaanerup ilimanassusaata qullasinnerulersissinnaanera.

Ilimagaarput imigassartortanngikkaluaraanniluunniit inuiaassuseq apeqqutaalluni aaversinnermi tinguup kisitsisai assigiinngissinnaamata. Tuniluuttumik tingulluummik tunillatsinnikut timimikkut misissortikkaluarlutik aaversikkaluarlutillu takuneqarsinnaavoq tunillatsinnikuuneq napparsimassutiginngikkaat. Misissuinitsinni paasivarput tuniluuttumik tingulluummik tunillatsissimasut inuunerat allanut sanilliullugit sivikinnerusoq. Taanna pillugu isumaliutigaarput tuniluuttumik tingulluummik tunillatsissimaneq siornatigut ilimagisamiit aarlerinarsinnaasumik nappaataasinnaamat.

Peqqissutsikkut sunniutit

Timikkut misissortinnermi tuniluuttumik tingullunneq type B eqqaamaneqartarnera annikilliartorpoq. Nalorninarpoq tingullunnerup kingunerisinnaasai toqussutigineqarsinnaasut nanineqartarnerlutik.

Tuniluuttumik tinugullunneq suli takussaavoq. Nunatsinni ineriartorneq malillugu periarfissaqarluarpoq tuniluuttumik tingulleq eqqumaffigineqarsinnaanera.

Periarfissat ilagai Kalaallit Nunatsinni nalunaarsorsimaffimmik katersuiffittaarneq. Paasissutissat tingulluummik tunillatsinnikunut tunillatsissimasinnaasullu nalunaarsorneqarsinnaaniassammata. Tassunga atatillugu atorneqarsinnaasoq ulluinnarni timikkut misissuinermi misissueqqisaarnernilu.

Tingullunnermik nappaateqarneq qanorlu katsorsarneqarsinnaanera eqqumaffigineqarnermi paasinninneq annertunerulersissinnaavaa. Taassumap kingunerisinnaavaa kingunerluutaasinnaasut ikilinerat.

Inuit siornatigut tuniluuttumik tingulluummik tunillatsissimanngitsut illersuutilatimmik kapitinneqartalinissaat siunissami kissaatigaarput.

Qinngorput, Nuuk, Greenland

ACKNOWLEDGEMENTS

Qujanaq (thank you),

Stig ”bow tie” Andersen for introducing me to research while I was a young medical student in Aarhus in Denmark sparkling my interest in research long before the initiation of this PhD study and still do when you come visit me and my family in Greenland. Your joy, your tireless approach and effort to research is enviable. Thank you Henrik Krarup for your humbling approach to research matters and sparing on academic or serious clinical matters on HBV and HDV-infected Greenlanders always having the human being in focus and hereby the ethical aspect. Thank you Peter Laurberg for your crisp and razor-sharp handling of research. Many tough questions we still would have loved your opinion on, but cannot due to your tragic passing. Your inspiration lives on. A collective thanks to you Stig, Henrik and Peter from my family for whom you came to visit in Greenland.

Qujanaq Michael Lynge Pedersen for your insight into pioneering monitoring programs in Greenland, for being my colleague and supervisor.

As anything free has been established from the hard work of others I gratefully acknowledge the permission and opportunity to use the data that has been collected and analyzed by my colleagues and friends, and also a great thanks for the access to health data from the Chief Medical Officer of Greenland, the Commission for Scientific Research in Greenland (KVUG)/ The Committee of Research Ethics in Greenland and the Board of Prevention and Health in Greenland.

A great thanks to you Gert Mulvad for supervising both my education in General Medicine and for being a moderator on getting time for research in a very busy schedule on every medical department in Greenland and also for always looking at

things from different angles precipitating the bright spots. Qujanaq Henning Sloth Petersen for your human approach to every Greenland patient and defining yourself as a clinician, although your research background and human nature was likewise admirable. You are dearly missed. Qujanaq Nikolaj Holm and Hanne Lynge Rex for all your help in translating the research materials into Greenlandic.

A thanks to Ingelise Leegaard helping on blood sampling and talks, to Anders Koch and members of the Greenland Medical Society for acknowledging my early work by awarding me with the Jens Peder Hart Hansen award.

A thanks to the heads and colleagues in all the clinical departments at Queen Ingrid's Hospital, Nuuk Health Care Centre, and Sisimiut Health Care Centre for letting me do research partly while running busy departments and to the University of Greenland for a quiet office ("the temple") with the best view in town (as I see it).

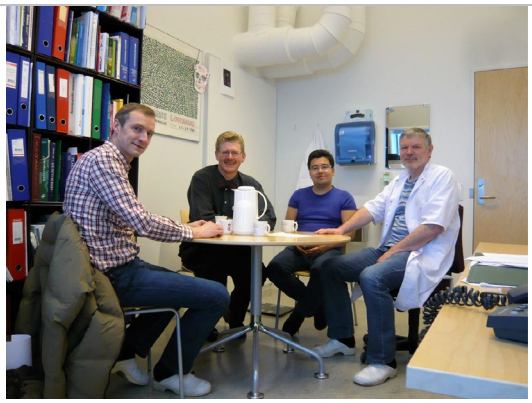
A warm, huge, and special thanks to my family, parents and brothers and to my dear "co-pilot" in clinical and private life my wife Hanne Lynge Rex and to my son Ulloriaq Rex for endless support, for patience and for everlasting encouragement.

A respectful thank you to my participants and to my patients.

Karsten Fleischer Rex

August 2019

Stig, Karsten & Henrik



Michael, Stig, Karsten & Gert

Greenland, Hanne & Ulloriaq

The work was made possible through funding from:

The Greenland Institute of Natural Resources and the Greenland Self-Government: Sundhedspuljen, and the Karen Elise Jensen Fund. The sponsors played no role in the study designs, the collection, analyses or interpretation of data or the writing of the thesis or papers.

TABLE OF CONTENTS

Kangerlussuaq, Greenland

ABBREVIATIONS

AIC	Akaike information criterion
Alb	Albumin
ALK	Alkaline phosphatase
ALT	Alanine aminotransferase
Anti-HBc	Antibody against hepatitis B core antigen
Anti-HBc-IgG	Immunoglobulin G antibody against HBcAg
Anti-HBc-IgM	Immunoglobulin M antibody against HBcAg
Anti-HBc-total	Immunoglobulin M and G against HBcAg
Anti-HBe	Antibody against hepatitis B e antigen
Anti-HBs	Antibody against hepatitis B surface antigen
AST	Aspartate aminotransferase
Bili	Bilirubin
BMI	Body mass index
CHB	Chronic hepatitis B
CI	Confidence interval
CT	Computer tomography
DCDR	The Danish Cancer and Death Registry
DNA	Deoxyribonucleic acid
EMR	Electronic medical records
ERCP	Endoscopic retrograde cholangio-pancreatography
GGT	Gamma glutamyltransferase
HAV	Hepatitis A virus
HBcAg	Hepatitis B core antigen

HBeAg	Hepatitis B e antigen
HBIG	Hepatitis B immune globulin
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HDV	Hepatitis D virus
HEV	Hepatitis E virus
HIV	Human immunodeficiency virus
HPV	Human papilloma virus
ICCH	International congress of circumpolar health
IDU	Intravenous drug users
IgG	Immunoglobulin G
IgM	Immunoglobulin M
LFTs	Liver function tests
MRCP	Magnetic resonance cholangio-pancreatography
NCRS	The National Civil Registration System
PCR	Polymerase chain reaction

Itilleq, Greenland

TABLE OF PUBLICATIONS

This PhD thesis is based on these papers

I	**Population-based comparative epidemiological survey of hepatitis B, D, and C among Inuit migrated to Denmark and in high endemic Greenland** Rex, Karsten Fleischer ; Krarup, Henrik Bygum ; Laurberg, Peter ; Andersen, Stig. Scandinavian Journal of Gastroenterology, 2012, Vol.47(6), p.692-701(1)
II	**Liver biochemistry and associations with alcohol intake, hepatitis B virus infection and Inuit ethnicity: a population-based comparative epidemiological survey in Greenland and Denmark** Rex, Karsten Fleischer; Krarup, Henrik Bygum ; Laurberg, Peter ; Andersen, Stig. International Journal of Circumpolar Health, 01 January 2016, Vol.75(1)(2).
III	**Reduced life span with chronic hepatitis B virus infection – a 10-year follow-up study in Greenland** Rex, Karsten Fleischer; Krarup, Henrik Bygum; Lynge Pedersen, Michael; Andersen, Stig. Submitted/in review (3)

CHAPTER 1. INTRODUCTION

This dissertation is based on research questions originating from clinical observations in relation to clinical work and living in Greenland.

Hepatitis B is a viral infection (HBV). Globally it is estimated that 257 million people are chronically infected with the virus (CHB) causing death to over 800,000 people in 2015 (4,5). The risk of dying because of CHB increases over time due to cirrhosis, end stage liver disease and liver cancer (hepatocellular carcinoma). HBV-infections are endemic in Greenland and earlier studies show a high prevalence of HCC, although this did not match the prevalence of HBV-infections (6). There is evidence that the risk of acquiring HCC or liver cirrhosis is related to genotypes of the HBV (7). Male gender, alcohol consumption, co-infections with additional viruses are other risk factors of HCC and liver cirrhosis on HBV-infection (7,8). Registers have inherent limitations on diagnosis and on causes of death, and HBV-infections have not been formally monitored in Greenland. The knowledge on the cause of HBV-infections in the Greenlandic population is therefore limited.

We made a cross sectional study among Greenlanders in Denmark (2) comparing the findings to a cross sectional study made in Greenland (1,2,9,10). Through a thorough review of all available electronic Medical Records (EMRs) and registries in Greenland we made a follow-up study on HBV-infections and on overall death on a cohort from Greenland (3). We did a systematic review on HBV-infections on Inuit in the circumpolar region (11). We helped work-up, monitoring and treating HBV-infected in Greenland.

CHAPTER 2. BACKGROUND

EPIDEMIOLOGY GLOBALLY AND IN GREENLAND

HBV-infection is a global health problem and may cause end-stage liver disease including liver cirrhosis and hepatocellular carcinoma. Due to the poor prognosis, HCC is the third most common cause of cancer related death. In the arctic region HBV-infection differs among indigenous peoples. HBV-infection is known to be endemic among the Arctic Inuit, but varies between Inuit populations (11). The burden of disease seem to vary in different regions of the world and in the circumpolar region (8). The concern on infection is also related to other risk factors such as co-infections, lifestyle factors, gender, age at infection and age, but also in relation to the type of HBV (8). In Inuit in regions of Greenland prevalence of HBV has been found to be as high as 29% (9). A more benign course of CHB has been suggested among HBV subtypes in Greenland and Canada due to a low registered incidence of HCC (6,9,12–14). Universal vaccination of newborns reduce spread of HBV and hereby the HBV related risk of HCC (15,16).

NATURAL HISTORY OF THE HBV

The Hepatitis B virus was first discovered in the 1960s (17,18). It was referred to as "serum hepatitis", and was associated to the "Australian Antigen" now known as the hepatitis B surface antigen (HBsAg). The structure of the hepatitis B virus has been investigated since discovery of its antigenic properties and through electron microscopy in the 1970s. Cloning and investigation of the viral genome has identified the HBV as a member of the Hepadnaviridae. The DNA encode structural viral proteins as well as a viral DNA polymerase. In the human body the viral proteins give rise to antigens. HBsAg and HBeAg (hepatitis B e antigen) can be detected I serum (19) as they are secreted from hepatocytes upon viral replication, while HBcAg (hepatitis B core antigen) can be detected in liver biopsies (20). The specific

immunoglobulin antibodies to the above mentioned antigens anti-HBs (antibody against HBsAg), anti-HBe (antibody against HBeAg), and anti-HBc (Immunoglobulin M antibody against HBcAg [anti-HBc-IgM], immunoglobulin G against HBcAg [anti-HBc-IgG] or total immunoglobulins against HBcAg [anti-HBc-total]) can be detected in serum in relation to infection (21,22).

The polymerase chain reaction (PCR) analysis method on amplifying small sections of HBV DNA has given an opportunity for further sensitive hepatitis B analysis on ongoing infections, genotyping and mutations. Also, the migration (routes of infection) of the HBV through continents on migration of infected people over the history of time can now be assed (23–25).
The overlapping reading frames in the HBV genome leads to constrains in possible mutations due to affection on more than one reading frame (26) yet, mutation rates are high compared to other DNA viruses (27).

Genome sequencing has led to classification of HBV into 10 genetic subtypes or genotypes (A-J) (21) based on more than 8% diversity on full genome sequencing or less than 4% diversity on S-gene sequencing and even further into sub-genotypes with a number attached to every genotype letter (example A1 or B5). Specific HBV sub-genotypes predominate in different parts of the world (8,21,25,26). The different genotypes and sub-genotypes are argued to have different potentials on degrees of inflammation and carcinogenic properties on the liver (8,21,28). In Greenland the sub-genotype B5 (formerly B6) predominates although more subtypes and genotypes (A,D) reside (9,29). B5 is argued to be a more benign genotype/ sub-genotype of HBV on both inflammation and carcinogenesis, although many aspects are not fully answered (8,9,25,28,30). The risk of a CHB carrier state is partly due to the age at infection. Vertical transmission of HBV from an infected mother to the child in the perinatal period is possible and the risk of chronicity on infection is reported to be as high as 90% (31). Risk of CHB due to horizontal

transmission of HBV during childhood has been stated to be 25% (32) while around 10% during adulthood (33).

HBV-infection does not cause liver injury by itself. Hepatic injury is related to the immune response. Different scoring systems of hepatic injury exist based on the degree of inflammation and scaring (fibrosis or cirrhosis) by visualization on liver histology (34). Histopathology is one way of evaluating degree of disease burden. The risk of HCC have been associated to different factors such as especially the viral genotype C, mutation in the Pre-Core or Core promotor regions and interpolation of HBV cccDNA into the host DNA. Also, host factors such as male gender with age above 40, family history of HCC, co-infection with hepatitis D or C virus, alcohol abuse and aflatoxin exposure are recognized risk factors. HCC usually develops in patients with liver cirrhosis (35). Factors of known importance on chronic inflammation and cirrhosis are HBV DNA load, high levels of HBsAg, HBeAg positivity and age at infection. It is still uncertain which risk factors play the major role in carcinogenesis (7,8). Liver cancer was predicted to be the sixth most commonly diagnosed cancer and the fourth leading cause of cancer death worldwide in 2018 (36).

Counting all available death certificates in a time period from 1995 through 2013 only seven have been registered to have died with or of a viral hepatitis according to the data bank from the National Board of Health in Greenland (37).

DIAGNOSTICS AND PHASES OF HBV DISEASE

Most HBV-infections progress without any clinical manifestation although infection can sometimes be diagnosed as an unspecified acute hepatitis with symptoms in forms of loss of appetite, dark urine, fever, joint pain, nausea and vomiting, fatigue and jaundice (38).

As no symptom is pathognomonic to only HBV-infection further diagnostics is needed to interpret the hepatitis disease. By time, serology, virology and by liver

biopsy hepatitis B can be divided into acute or chronic hepatitis B infection and can be further specified into theoretical infectious phases (22).

Based on serological findings and a time period of infection lasting less than six months an acute hepatitis can be defined (39). CHB is divided into different phases based on serology, aspartate transaminase (ALT) levels in serum and liver biopsy findings (21,40). These phases are further contemplated on in relation to treatment. The formal goal of treatment on CHB-infection is to reduce the risk of liver disease, liver failure and HCC. Anti-viral therapy is used to reduce burden of disease in case of an immune reactive phase or upon reactivation to prevent aggravation in inflammation and fibrosis of the liver (21,41).

Earlier studies have suggested immune tolerant or inactive phases among Inuit in Greenland (42–44) although very few studies have interpolated liver function tests in their HBV-studies (9,45) and till this date none on liver biopsies.

Patients with immune-tolerant CHB-infection and without treatment are suggested to be monitored at least every six months with serum ALT (30). Anti-viral treatment should be considered on behalf of ALT, viral load and on liver biopsy evaluation if attainable (21,30).

THE SETTING

Eighty-one percent of Greenland is covered by ice (the Greenland ice sheet). All towns and settlements are located along the coastal line. No roads exist between towns or settlements. Travel is only possible by water or air and with seasonal differences. Domestic transportation types include plane, helicopter, snowmobile, dogsleds and boats (46). Greenland is a self-governing region within the Kingdom of Denmark. Greenland became a Danish colony in 1721 and a Danish County in 1953. A Greenland Home Rule Government was established in 1979. Self-rule was established on June 21th 2009 (47). Citizens of Greenland still have Danish

citizenship. The population density is the lowest in the world. The population in Greenland is around 56-57000. Most are of Inuit descent (Thule culture/Neo-Eskimo) while a minority are migrants from Denmark (mostly Caucasian) (48). Approximately 6-7000 people in Greenland were born outside Greenland (most of these born in Denmark). Around 13-18,000 persons in Denmark have been defined as being of Greenlandic descent (2,47).

On aspects of blood borne diseases Intravenous drug use has been considered nonexistent in Greenland before (49,50) and current injecting drug users (IDU) are still not part of present clinical practice (personal report from Karsten Rex [KR]). On venereal diseases gonorrhea and chlamydia infections are still a major problem in Greenland (51). Hepatitis B is one of many known infectious hepatotropic viruses of which some reside in Greenland. Other hepatotropic viruses have been recorded in Greenland including the hepatitis A (HAV), D (HDV), E (HEV) and C virus (HCV) (29,45,49). Alcohol use has been associated to health problems and deaths, although very little research exist on liver disease on the basis of alcohol consumption among Inuit (52–55). Risk of liver disease on alcohol consumption may rise with viral hepatitis (56,57).

All health care services are publicly funded in Greenland. These include free vaccinations, treatments and all visits to the health care providers.

HBV-VIRUS INFECTIONS IN GREENLAND

The first introduction of HBV (Genotype B5) into the population of Greenland dates back to the very first Thule-peoples migration to Greenland from the Bering Strait region approximately 900 to 700 years before present (25). Earlier studies dating back to the 1970s have shown endemicity in different parts of Greenland (11,42–44,49). Studies have hinted a benign course of disease (9,12,58). Infections with hepatitis D virus (HDV) has been studied to some degree earlier (29,42) and caused concern (45). HBV- and HDV-infections among Greenland migrants have not been

studied (1,59). It is debated how HBV-infections are transmitted in general in the Greenland population. HBV transmission during pregnancy, childbirth and horizontally due to housing conditions or sexually is plausible and might differ according to place and regions (9,42,43,45,49,51). As mentioned intravenous drug use is nonexistent in Greenland and disease transmission today due to contaminated blood products and needle sharing among Greenlanders in Greenland is not likely (1,42). Blood borne diseases can be introduced to Greenland on migration (1,50,60). Through decades guides on blood transfusions in Greenland have been updated now containing screening for HBV, although transmissions by way of this route has been possible (61).

New-born and childhood vaccination programs in Greenland have differed over the last decades with the introduction of the HBV vaccine in 2010 (12,61–63). Vaccination coverage is largely unknown (62). Screening of HBV on pregnant women has been ongoing since the 1990s (12) with the availability of vaccination and HBIG administration to the newborn.

Until this day there is no nation-wide monitoring-program on HBV in Greenland. Although there has been intentions to initiate such a program, this has not been set up. Despite recommendation, there has been no official guideline internally in Greenland for screening, diagnostic work-up and follow-up, although treatment today follows international guidelines. There has been limitations in the paraclinical assessment of HBV in Greenland.

Reporting of acute and CHB is mandatory in Greenland. Pregnant women, blood donors and patient who are to undergo chemotherapy or immunosuppressive treatment are to be tested for HBV infection status (11). Antiviral treatment is usually not limited to the accessibility of medicine (60) which is as mentioned earlier cost free for the individual and also comparable to international guidelines (21,30).

Nuuk fjords, Greenland

CHAPTER 3. HYPOTHESIS AND AIMS

A unique benign long-term outcome of HBV-infection has been suggested in Greenland, as described in detail earlier. A systematic follow-up on the HBV-infected in general or in studies, the influence of migration on HBV prevalence, and hereby the selection of survivors on HBV-infection has not been thoroughly explored. The overall aim of this PhD study was to elucidate disease burden of HBV-infection in a Greenlandic population in Greenland and in Denmark. This assessed by comparing Greenlanders with frequent HBV-infections from a cross sectional study in 1998 in Greenland to migrated Inuit Greenlanders from a subsequent cross-sectional study in Denmark in 2006. In addition, assessing overall survival and disease burden over a course of ten years. This through a thorough systematic review of all EMRs and registers on attenders from the 1998 cross-sectional study in Greenland also taking into account health factors such as diet, smoking, alcohol intake, body mass index and liver function tests from the clinical study. A secondarily aim was to cultivate an idea for a future monitoring program and containment of HBV-infections in Greenland while working in a Greenlandic environment. The PhD dissertation comprise primarily of three individual studies, addressing specific aspects of the above.

1. The aim was to report prevalences of serological markers on hepatitis B, D, and C virus infections among Greenlanders living in Greenland and who had migrated to Denmark, also taking into account objective measures of hepatic disease (study 1 (1)).

2. The aim was to describe associations between liver biochemistry, reported alcohol intake and HBV-infection, also taking into account ethnicity, BMI, gender, age and diet in an Arctic population (study 2 (2)).

3. The aim was to do a 10-year follow-up study on a population of Greenlanders with frequent HBV-infections concerning hepatitis B diagnostics, cirrhosis, end stage liver disease, HCC, vaccinations, other liver diseases and all-cause death using all available EMRs and registries from Greenland. Also, linking clinical study results on HBV-status, liver

function tests, smoking habits, drinking habits, diet and body build measures to all-cause mortality analyses (study 3 (3)).

In addition, monitoring aspects and containment of HBV-infections were met talking to medical personnel that had been working on Hepatitis B in Greenland and in the Arctic during the latest decades trying to enhance diagnostics and work-up possibilities. Moreover, by working in different parts of Greenland and with hepatitis patients from all over Greenland during the course of the 5-year part time PhD and beyond.

Aalborg, Denmark and Nuuk, Greenland

CHAPTER 4. METHODS

STUDY AREA AND POPULATIONS

EAST AND WEST GREENLAND

Participants in Greenland were men and women aged 50 through 69 years in 1998. Eligible persons were identified through the National Civil Registration System (NCRS) where all persons born in "The kingdom of Denmark": Denmark, the Faeroe Islands and Greenland are recorded. A random sample of 25% of men and women living in Nuuk in West Greenland were identified and invited to be part of the investigation (total population 12,909; in the age group 1,920; year 1998) (10). All inhabitants in this age group living in the town of Tasiilaq (total population 1,724; in the selected age group 184; year 1998) or in the surrounding settlements (n=152) (Tiniteqilaaq, Sermiligaaq, Kulusuk and Kuummiut) in East Greenland were invited (total population 1,093; in this age group 152; year 1998). The potential participants in Nuuk had initially been selected using the hospital registration system in Nuuk in 1998 on which 1920 persons were recorded. This had not been updated and the selection was validated by comparing it to the National Civil Registration System (NCRS). Of the 480 persons initially selected in Nuuk 255 persons had moved or died and therefore could not be contacted on the registered addresses and therefore not found eligible for the study. Of the remaining 225 persons, only 14 refrained from attending (6%). In East Greenland, the NCRS was used in both the settlements and in the town and only nine persons out of 161 potential participants from the settlements and 13 out of 197 potential participants from the town were not eligible due to latency in reporting of death or changing of addresses. This was validated by the local porter or the village health care provider. Only one refrained from attending in the settlements (0.7%) and 11 (6%) from the East Greenlandic town Tasiilaq. In total 535 persons participated out of 561 invited in Greenland.

SAs ticket receipt to Greenland anno 1998

DENMARK

For the cross-sectional survey in Denmark in 2006 (from two major counties Aarhus and Aalborg in Jutland) individuals born in Greenland with at least one parent born in Greenland were included. Moreover, Greenlanders aged 40 through 49 years were included on basis of the Greenlandic population size in the regions investigated. In total 312 subjects born in Greenland were identified through the NCRS. We were able to establish contact to 220 subjects. Here, 54 persons were excluded on basis of the inclusion criteria and 30 eligible participants refrained. We could not establish contact to 92 subjects. Of the 136 Inuit investigated in Denmark 37 were aged 40 through 49 years.

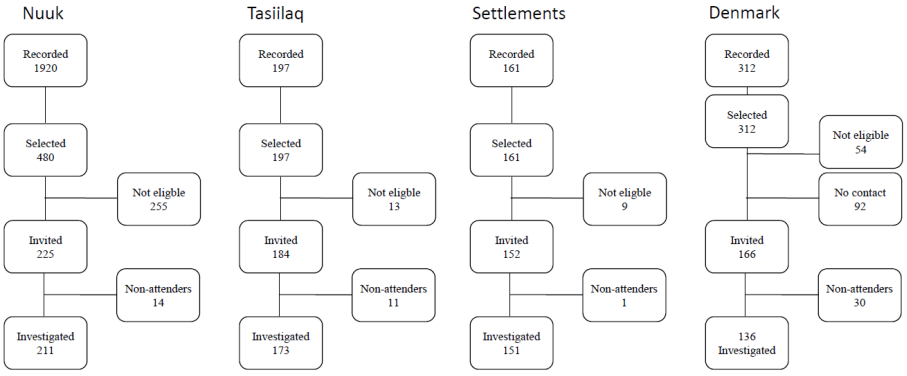


Figure 1. Flow-charts of inclusion of participants in Greenland in 1998 and in Denmark in 2006

Eligibility for the 10-year (registry) follow-up study relied on informed consent from the 1998 clinical study in Greenland.

INVESTIGATIONAL PROCEDURES

A letter of invitation was delivered to each subject by the local hospital porter or the nursing station attendant in Greenland while using the Danish postal service in

Denmark. Non-responders were invited three times. The investigation took place at the local hospital or nursing station or, by request, at home visits. A physical examination and venous blood sampling was performed by one of the investigating doctors Stig Andersen (SA) or Peter Laurberg (PL), by Bodil Hvingel (BH) in Greenland and by KR and SA in Denmark. Examination included height without shoes, weight in indoor clothing, any major disabilities, scleral jaundice, spider naevi and signs of hepatic decompensation such as confusion, jaundice, fluid retention and cachexia. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Participants were interviewed by an interpreter or by one of the investigational physicians, who completed the questionnaire in either Danish or Greenlandic, as appropriate for the subject. The same interpreter Karoline Berglund was used in Nuuk, Tasiilaq, and all settlements. Information on lifestyle patterns and dietary habits was obtained by using questionnaires. Questions were asked as written in the questionnaires.

ALCOHOL

Twelve grams of alcohol was the equivalent of one unit. Average alcohol intake above two units per day for women and three for men defined an intake above the recommended levels. Alcohol intake was also categorized into two groups (never/ever) and five groups (never, drinks 0-7 units weekly, drinks 8-14 units weekly, drinks 15-21 units weekly and drinks >21 units weekly).

DIETARY HABITS

Participants were classified based on the number of days per week that the main meal consisted of Greenlandic food items (that is, Greenlandic seal, whale, wild fowl, fish, reindeer, musk ox and hare) (10).

SMOKING

Smoking was categorized into either two groups (never smoked/have smoked) or five groups (never smoked, ex-smoker, has <10 cigarettes daily, has 10-20 cigarettes daily and has >20 cigarettes daily).

INUIT ANCESTRY

Inuit ancestry was defined as being born in Greenland and having had at least one parent born in Greenland.

BODY MASS INDEX

Body mass index (BMI) was calculated as the weight (in kilograms) divided by the height (in squared meters). A BMI below 18.5 kg/m^2 was defined as low, and a BMI above 25 kg/m^2 was defined as high. A BMI between 18.5-25 kg/m^2 was categorized as normal (64).

VENIPUNCTURE

A venous blood sample was drawn using minimal tourniquet, separated and stored at -20 C. Blood samples were blinded using an 8-digit code, and analyzed in random order. Blood sampling was omitted with four participants in Denmark and with one in Greenland, in compliance with the participants' choice.

CLASSIFICATION OF HEPATITIS EXPOSITION

The participants were classified, based on HBV serology analyses, as being currently infected (if HBsAg was positive), as having been previously exposed (if HBsAg was negative and anti-HBs and/or anti-HBc-total were positive [due to a lack of HBV-vaccination in this population in this time-period]) and as being never exposed (if all of the markers were negative) (1,9).

DATA SOURCES AND REGISTRIES

Due to the blinding of individual identification after the first cross-sectional study, the Population Registry of Greenland ('Sundhedsbasen') was used to find every participant's ten digit Danish Social Security Number for subsequent register analysis. This done through the linking of names, age and address at time of investigation of every participant to a specific social security number. A social security number could be addressed strictly to all but two participants from the cohort, for whom register data hereby could not be achieved. EMRs and registries were accessible and manageable. The earliest documentation in the EMRs in Greenland were from the late 1990s. These included radiological scans ('Infinnitt system') and descriptions ('Infinnitt', 'Æskulap lægeklinikken'), old ('Æskulap Lægeklinikken', 'Æskulap Tasiilaq', 'Journaler i word') and the new joined EMRs ('Cosmic') in Greenland as well as the nation-wide electronic available blood sample analysis platform ('BCC-lab'). Register data from the Danish Biopsy Registry ('Pato Bank') was accessible and also from the Danish Death Registry ('dødsårsagsregisteret') through the Chief Medical Officer of Greenland. The documentation of death causes from Greenland into the Danish Death Registry has been ongoing since 1973 in Denmark with addition of death causes from Greenland in 1983 (65). The Danish Biopsy Registry was established in the 1970s, although nation-wide registry was not implemented until 1997 (66).

LABORATORY ANALYSIS

SEROLOGY, VIROLOGY, HBV GENOTYPING, QUANTIFICATION OF HDV AND HCV, AND BIOCHEMISTRY

Serology, virology, HBV genotyping, quantification of HDV and HCV, and biochemistry has been described in detail in earlier reports (1,9,67–69).

STATISTICAL ANALYSES

Random selection of participants in Nuuk was done using MedStat (Astra, Albertslund, Denmark). Data were processed and analyzed using Corel Quattro Pro X3 (Corel Corporation, Ottawa, Ontario, Canada), the Statistical Package for the Social Sciences version 13.0 (SPSS Inc., Chicago, Ill., USA), using Stata version 15.0 Statistics/Data Analysis (Texas StataCorp, USA) and Microsoft Excel 2016. Statistical significance was considered on the basis of a 2-sided p-value of 0.05 and 95% confidence intervals (70,71). Data were provided as medians with 25^{th} and 75^{th} percentiles when they did not follow the normal distribution. Chi-squared test was

used for comparison of proportions and Mann–Whitney U-test (Wilcoxon rank-sum test) for comparison of median values.

Statistics for the individual studies has been described in detail in our earlier reports (1,2). In short, multivariate logistic regression models were used in elucidating factors of importance concerning HBV exposure and multivariate linear regression models on factors on LFT levels.

Moreover, entry and exit time (time of censoring or death) for survival in study 3 were established according to the clinical study in Greenland. Entry time for participants from Nuuk was on June 20th 1998 and for participants from East Greenland on November 16th 1998. Censoring time being a ten-year follow up. Date of death was manually extracted from the Greenland Population Registry, the EMRs and these data were cross-validated with the Danish Cancer and Death Registry (DCDR). The specific registered causes of death were obtained from the DCDR (3).

Logical, potential accessible predictors (covariates in multivariate survival analyses) of time until death were obtained from the clinical cross-sectional study. The stepwise function was computed in Stata (significance level 0.2) for calculation of covariates of significance, but ultimately not used in model fitting due to the risk of overfitting. The covariates that were used in analyses of survival included age in years (a continuous variable), Inuit origin (yes/no), place of living (West or East Greenland), gender (male/female), diet categorized into two groups (main meals dominated by Greenlandic food items: yes/no), liver function tests (continuous variables), BMI (a continuous variable or in the categories mentioned above), alcohol intake (in the categories mentioned above), smoking status (in the categories mentioned above) and HBsAg (yes/no) or HBV-infection status in three categories (present, past or never) (3).

The data distribution that assessed outliers, normality, collinearity and multicollinearity was evaluated by using Q-Q plots, the Shapiro-Wilk W test,

correlation tests and visual plots (multicollinearity automatically, collinearity by the pwcorr command and visually by the graph matrix command in Stata). The possible transformation to normality or categorization was also evaluated. Incidence rates, incidence rate ratios and hazard ratios were estimated based on infection status. Dates of birth were used as a left truncation point (using age as an underlying time scale) in the adjusted survival analyses also to control for confounding by age. Before Cox-regression assumptions on non-informative censoring was tested and met. The proportional hazard assumption on infection status was assessed and met using plotted cumulative hazard estimates (Nelson-Aalen Cumulative hazard estimates) on a log scale (log-log plot of survival, stphplot in Stata), and formally tested using Schoenfeld residuals testing (estat phtest in Stata) (3).

Confounding effects and interactions of possible predictors (gender, alcohol, BMI, Inuit ancestry, place of living, smoking, diet and high age) on infection status and death were tested using the Mantel-Haenszel and Mantel–Cox methods. Effect modification on infection and death was tested using predictor as an interaction term in Cox analysis. Adjusted cox-models with confounding variables and interactions were compared for enhanced statistical explanation using Likelihood-ratio tests for nested models (3).

Parametric model fit and PH assumption was evaluated visually through a 'log (-log(predicted survival)) plot' on infection status. Available parametric functions were compared with the Akaike information criterion (AIC) for relative model quality. Martingale residuals were estimated and plotted against the linear predictor/covariate for detection of outliers. Cox-Snell residuals were visualized in histograms for normality and plotted against cumulative hazard function for visualizing model fit. Deviance residuals for uncensored data were plotted against the linear prediction to visualize homoscedasticity, outliers and model fit for parametric models. Fitting of parametric models were primarily done for an explanatory model and used (with precaution) on a prediction model for computing

predicted median lifetime differences on infection status. The Weibull function for the adjusted parametric regression survival analysis had the best fit judging on AIC and residuals when compared to other possibilities using Stata, and was used in estimating predicted median survival times. Participants were divided into subgroups based on place of living and ethnic origin in attempt to further examine potential regional differences (confounding) on survival. Missing data was looked at on every step of statistical analyses (3).

ETHICS

The studies were conducted according to the guidelines laid down by the Declaration of Helsinki. The regional ethics committee for Viborg and Nordjylland County approved the study in Denmark (VN-20060038). Ethical approval was obtained for the initial study from the Commission for Scientific Research in Greenland in 1998 (j.no. 505-31), with supplementary approval for hepatitis diagnostics in 2004 (J.no.505-99). The Committee of Research Ethics in Greenland granted acceptance of the register study for follow-up on the cohort population as did the Chief Medical Officer of Greenland (KVUG ref.no. 2016-20). The Board of Prevention and Health in Greenland approved and supported access to health data from the EMRs (November 3rd 2016). All subjects gave informed written consent in the clinical studies in Danish or Greenlandic by participant choice.

MONITORING HEPATITIS IN GREENLAND

Aspects on monitoring HBV-infected in Greenland relied on clinical work in Greenland from 2010 and onward. HBV and HDV problematics from all over Greenland were handled with correspondence with hepatitis experts from Denmark and from the circumpolar region. A systematic review on HBV diagnostics, vaccination, treatment options and future assessment on HBV in Greenland and status in the circumpolar region was assessed (11). Research aspects on monitoring

capabilities on indicators for other diseases using the different EMRs in Greenland was assessed (72).

Nuuk, Greenland

Itilleq, Greenland

CHAPTER 5. RESULTS

STUDY 1: SEROLOGICAL MARKERS OF HEPATITIS B, D AND C VIRUS INFECTION AMONG GREENLANDERS IN GREENLAND AND DENMARK

In study 1 prevalences of serological markers of hepatitis B, D, and C virus infection among Greenlanders living in Greenland and who had migrated to Denmark was surveyed also taking into account objective measures of hepatic disease, lifestyle factors and comparing weight, height and liver function tests on infection status (1).

INVESTIGATION IN GREENLAND

Participation rate in the population-based survey in 1998 in Greenland was 95%.

Table 1 includes the descriptive data of participants from Greenland (3).

More non-Inuit were men ($p<0.001$) living in one of the investigated towns ($p<0.001$) in concordance with the demography in Greenland (migrant work force with male non-Inuit predominance). All but seven Inuit had both parents born in Greenland and one female in this group had an ongoing HBV-infection.

Serological signs of hepatitis B exposure are shown in Table 1 (1,3). None had signs of liver disease on the physical examination.

The absolute and relative number of hepatitis B infected differed among genders with the highest number of infected among male Inuit in settlements on the east coast (29 infected, 34.5% of Inuit in settlements in the age group). Inuit males or females from villages comprised approximately the same proportion on overall percentages on gender (Inuit males from villages represent 27.2% of all males while Inuit women from settlements represent 27.9%). Although, there was no significant difference on distribution of ongoing HBV-infection between genders (Inuit) in the settlements (p-value 0.105) on chi-squared testing. Distribution on markers of HBV-

infection did differ on gender in both towns (Nuuk, p=0.027 and Tasiilaq, p=0.046) while not in the villages (p=0.81).

Table 1. Characteristics of participants from West and East Greenland (3).

	Inuit	Non-Inuit	All
All (n)	441	94	535
Gender (n)			
Men	234	75	309
Women	207	19	226
Age			
n, <58 years	207	69	276
n, 58+ years	233	26	259
median (25; 75%tile)	58 (54; 63)	56 (53; 58)	57 (54; 63)
Smoking (n)			
Never	57	25	82
former	50	17	67
<10	188	10	198
10 to 20	126	29	155
>20	19	13	32
missing	1	0	1
Alcohol (n)			
Never	131	9	140
0-7	148	42	190
8-14	96	24	120
15-21	39	6	45
21+	19	12	31
missing	8	1	9
BMI groups (n)			
<18.5	27	1	28
18.5-25	208	35	243
>25	176	57	233
missing	30	1	31
HBV (n)			
Current	87	0	87
Former	247	23	270
Never	104	70	174
missing	3	1	4
Died before follow-up (n)[a]	166	15	181
unknown	2	0	2
Moved out of Greenland (n)[a]	6	25	31
Men	1	17	18
Women	5	8	13

[a]On a 10-year follow up

Moreover, there was no gender difference among Non-Inuit on markers of HBV-infection (p=0.930). One fourth of both genders had markers of HBV (all born in Denmark). Only one (man) had a history of HBV-vaccination going through the Greenlandic EMRs. On Anti-HBc-total serology 11% of non-Inuit women (n=2 out of 18) while 21% (n=16 out 75) of Non-Inuit males were positive. Sixty-one participants were HBV-DNA positive, 38 million copies/mL was the highest viral count and genotype B predominated (9). Five had a positive anti-HDV and none with measurable HDV-RNA (1).

INVESTIGATION IN DENMARK

The participation rate in Denmark was 52.2%. Of the 136 participants, 33 were men and 110 had both parents born in Greenland. Three had a history of earlier intravenous drug use (1).

Overall median (25^{th}; 75^{th} percentiles) age at sexual debut among Greenlanders in Denmark was reported to be 16 (15; 17) with missing data on 13, while debut was 14 years to 18 years among the 5 infected with missing data on one participant and 15 (15; 17) among never exposed. Between genders median age for reported sexual debut was 15 (15; 17) for men and 16 (15; 17) for women. Number of sexual contacts did not differ between genders overall on a 12 month period (p=0.61), with only 6 persons having more than one sexual partner, although ranges for men were null through 30 and null through 6 for women.

Few had yellowing of the sclera (eight participants) or spider neavi (one participant), and these signs did not associate to HBV-infection. No participant had signs of decompensation. There was no statistical association between reported hepatitis or vaccination and serological markers on HBV "(p=0.69 and p=0.86)" (Rex et al. 2012, 695) (1).

Anti-HDV was found in only one participant. Exposure to both HBV and HCV was found in one participant.

HBsAg was found positive in five women and one man and none were exposed to HDV or HCV (1). Range of HBV-DNA was null to 200 copies/mL. We found no clinical signs of disease on these and no difference on LFTs or body build when comparing participants on HBV infection status (never, past, present) (1).

OVERALL ON HBV

No associations were found between measurable parameters used in the clinical studies and current HBV infection in the crude comparisons or in the multivariate linear regression models (1). Markers on HBV in the studied migrated Greenlandic population in Denmark resembled the population studied in Greenland with no statistical difference on prevalences (1).

STUDY 2: ASSOCIATIONS TO LIVER BIOCHEMISTRY

Study 2 aimed to describe associations between liver biochemistry, reported alcohol intake and HBV-infection, also taking into account ethnicity, BMI, gender, age and diet among participants from study 1 (2).

Overall, data on 671 participants were investigated. Alcohol consumption was more prone among non-Inuit (90%) than Inuit (70%). Among Inuit participants East Greenlanders had the highest alcohol intake while the lowest consumption was in Nuuk (the capital) (2).

HBV, BMI and alcohol (also on behalf of below/above recommended consumption) distributions did not differ on participants from Denmark when grouping them into two age groups (below or above age 50 years), although distribution on gender was different ($p=0.007$).

Multivariate linear regression models on the 441 Inuit and 94 non-Inuit participants from Greenland (not on participants from Denmark as biochemical analyses were done separately) showed evidence of increasing AST and GGT, and decreasing ALK on alcohol consumption (2). Non-Inuit origin showed evidence of lower AST ($p<0.001$), GGT ($p<0.001$) and ALK ($p<0.001$) compared to Inuit (2). Advancing age increased bilirubin ($p<0.007$). Female gender was associated to lower AST ($p<0.04$) and GGT ($p<0.052$). Consumption of traditional Greenlandic diet showed evidence of higher ALK ($p<0.001$) and lower albumin ($p<0.001$) (2).

Increasing BMI associated with higher AST ($p<0.013$), GGT ($p<0.001$) and albumin (0.007). None of the above mentioned factors associated with LFTs on other analyses and importantly neither did infection with HBV (2).

Multivariate logistic regression analyses showed Inuit origin to be associated with GGT above normal "($p<0.001$; odds ratio (OR), 95% CI:8.8, 3.8-21)" (Rex et al. 2016, 6) (2). Also, increasing BMI and alcohol consumption was correlated to high GGT (2). AST above normal for each gender correlated to alcohol consumption and Inuit ethnicity. Current infection with HBV did not correlate to abnormal AST (or any LFT) or modified the association between AST and alcohol consumption (2). Only Inuit origin seemed to be an effect modifier on AST alone, while not on any other LFT (2).

STUDY 3: A 10-YEAR FOLLOW-UP ON GREENLANDERS WITH FREQUENT HBV-INFECTIONS

In study 3 the aim was to do a 10-year follow-up study on the population of Greenlanders from Greenland investigated in Study 1 concerning hepatitis B diagnostics, cirrhosis, end stage liver disease, HCC, vaccinations, other liver diseases and all-cause death using all available EMRs and registries from Greenland. Also, linking clinical study results on HBV-status, LFTs, smoking habits and drinking habits, diet and body measures to all-cause mortality analyses (3).

The characteristics of participants is presented in Table 1 (3). A flowchart of the participants is shown in figure 2. One third of the total cohort had died during the 10-year follow-up period. Thus, there were 181 events (deaths) (34%) and 352 censored (66%) as 352 were known to be alive at follow-up.

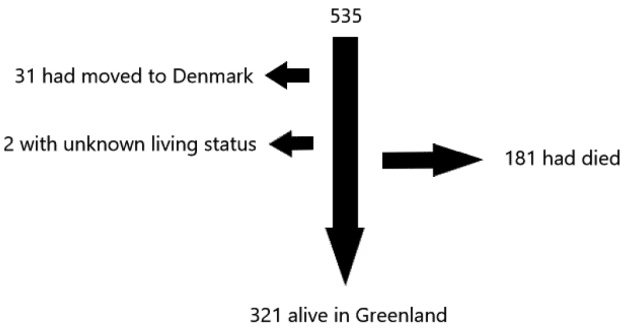


Figure 2. Flowchart on a 10-year (Register and EMR) follow-up.

As previously described, the 1998 cross-sectional study had a participation rate of 95%. Blood samples were obtained from 531 of the 535 individuals, and 87 individuals were HBsAg positive. All but one of the individuals were also anti-HBe positive.

REGISTERED CAUSES OF DEATH

The causes of death did not differ according to HBV infection status, as is presented in Table 2 (3). Forty-five out of the 87 individuals who were diagnosed with HBV-infections had died at the time of the 10-year follow-up, compared to 136 of the 442 noninfected individuals (52% vs 31%, $p<0.001$). Causes of death could not be determined from the death registry in nine patients. There were no recordings of HCC in the registries, but one patient without HBV-infection had HCC with metastasis to the lung, according to the pathology report (3).

Table 2. Causes of death in subjects with and without HBV-infection as reported in registries (3)

	Infected	Non-infected	p-value
Total number of deaths	45	136	<0.001
Registered causes of death:			
Uppper Airway and Gastro Intestinal cancer	5	15	ns
Lung cancer	12	28 [a]	ns
Myelomatosis, Prostatate and Retroperitoneal cancers	0	3	-
Kidney cancer	1	1	-
Uterine Cancer	0	4	-
Ovarian Cancer	1	0	-
Unspecified cancer	1	5	-
Apoplexia cerebri/Subarachnoidal hemorrhage	1	3	-
Epileptic	1	0	-
Heart Disease	4	12	ns
Chronic Lung Diseases	7	14	ns
Bile Duct Obstruction	1	1	-
Pyelonefritis	1	0	-
Thrombosis	1	0	-
AIDS	0	2	-
Accidents, Alcohol related, Hypothermia, Suicide	7	17	ns
Other [b]	1	23	p<0.05
Not registered	1	8	ns

[a] According to the EMR, one incidence of lung cancer was a metastasis from hepatocellular carcinoma

[b] Botulism, Septic Shock, Kidney Problems, Diabetes, Anaemia, Cachexia, Tuberculosis, Meningeoma

REGISTER-BASED HBV DIAGNOSIS, KNOWN LIVER DISEASES AND VACCINATION

None of the 533 participants had a registered HBV vaccination, and none had liver disease by 1998, according to the EMR and in compliance with the cross-sectional study. One participant had been screened for hepatitis and was documented to be HBsAg negative in 1998 according to the EMRs. Eight EMRs mentioned an HBV screening. One case was HBV positive in 2005 and one case was HBV positive in 2008. One participant (who was HBV negative in 1998) was stated to have alcoholic liver cirrhosis, based on a history of alcohol use, and an ultrasonography of the liver that showed dilated bile ducts. However, a computer tomography scan (CT scan) report

demonstrated no signs of liver disease. An HBV diagnostic work-up was stated, but results were not reported in the EMR. One participant (HBV negative in both 1998 and 2008, according to the EMR) had cholestatic hepatitis, according to a liver biopsy**.** One participant was recorded as being HBV vaccinated by 2008 (3).

HBV AND PREDICTORS

HBV-infection status proportions did not differ with gender, BMI group or smoking habits, whereas it differed with alcohol consumption ($p=0.025$), ethnic origin ($p<0.001$; no non-Inuit participants were infected), diet ($p=0.002$), age ($p=0.009$), being a smoker ($p=0.016$) and place of living (east/west; $p<0.001$) (3).

ASSOCIATIONS TO DEATH

Death was associated with HBV-infection ($p<0.001$), smoking status ($p=0.004$), origin ($p<0.001$), age (above a median of 57 years, $p=0.009$), diet ($p=0.018$) and alcohol status (do drink vs never drink, $p=0.004$) but was not associated with place of living ($p=0.08$) or gender ($p=0.96$) (3).

SURVIVAL ANALYSIS

Table 3 presents the difference in survival among participants with and without HBV-infections.

Table 3. Survival data on Greenlanders in Greenland followed up for 10 years.

	infected	Non-infected	Total
All participants	87	446	533
Non-parametric analysis			
Number of events	45	136	181
Expected number of events	26	155	
Median survival time (lifetime in years)[a]	67.8 (61.8; 72.1)	71.7 (64.0; 79.3)	70.7 (63.4; 77.1)
Death rate per 1000 person-years (disease burden)[b]	72.77 (54.34-97.47)	36.31 (30.70-42.96)	41.48 (35.86 -47.98)
Incidence rate[b]	0.073 (0.054-0.098)	0.036 (0.031-0.043)	
Incidence rate ratio (IRR)[b]	2.00 (1.40-2.83)		
Risk ratio (hazard ratio)[b]	1.70 (1.33-2.17)		
Logrank test	P<0.0001		
Semi-parametric			
Adjusted hazard ratio[c]	1.57 (1.07-2.30)		
Parametric analysis			
Predicted median survival in years[a]	64.8 (63.3; 66.9)	71.8 (68.8; 75.3)	70.6 (67.3;74.6)
Predicted median survival time difference in years[a]	6.9 (3.2; 10.9)		
Predicted median survival time difference in years[d]	6.6		
Adjusted hazard ratio[e]	1.72 (1.20-2.46)		
Only eastgreenlandic Inuit			
Participants	83	204	287
Non-parametric			
Number of events	42	72	114
Expected number of events	31	83	
Median survival time (lifetime in years)[a]	68.60 (61.81; 72.87)	69.5 (60.13; 75.63)	69.03 (60.62; 75.26)
Death rate per 1000 person-years (disease burden)[b]	69.96 (51.71-94.67)	45.92 (36.45-57.86)	52.58 (43.76-63.18)
Incidence rate[b]	0.070 (0.052-0.095)	0.046 (0.036-0.058)	0.053 (0.044- 0.063)
Incidence rate ratio (IRR)[b]	1.52 (1.02-2.26)		
Risk ratio (hazard ratio)[b]	1.43 (1.08-1.90)		
Logrank test	P=0.0232		
Semi-parametric			
Adjusted hazard ratio[c]	1.55 (1.05-2.32)		
Parametric			
Predicted median survival in years[a]	64.9 (62.7; 67.3)	69.2 (66.2; 72.6)	67.8 (64.8; 70.9)
Predicted median survival time difference in yers[a]		4.5 (0.8; 8.5)	
Predicted median survival time difference in years[d]		4.1	
Adjusted hazard ratio[e]	1.59 (1.07-2.36)		

[a]Median values (25-; 75-percentiles)
[b]95% confidence intervals
[c]Adjusted cox-regression
[d]If only taking infection status into account
[e]Adjusted weibull-regression

Survival differed markedly with HBV-infection (log-rank test for equality; p<0.001). The unadjusted overall median (25th; 75th percentiles) survival time was 70.7 years (63.4; 77.1). The median survival time was 67.8 years (61.8; 72.1) for the infected patients and 71.7 years (64.0; 79.3) for the noninfected patients. The risk ratio was 1.70 (95% CI: 1.33-2.17) for the infection status. The hazard ratio was 2.03 (95% CI: 1.44 -2.85) among the infected patients (p<0.001) when using only HBV-infection status in the Cox model (3).

The hazard ratios (HR) for the adjusted cox regression analyses were higher with infection status (HR: 1.57; 95% CI: 1.07-2.30) and with smoking status (HR: 1.92; 95%

CI: 1.07-3.42). The HR for the adjusted Weibull regression model on infection status was 1.72 (95% CI: 1.20-2.46) (3).

The overall adjusted predicted median survival time (predicted life span) was 70.6 years (67.3; 74.6). The predicted life span was 64.8 years (63.3; 66.9) among the infected patients and 71.8 years (68.8; 75.3) among the noninfected patients. The median predicted lifetime difference was 6.9 years (3.2; 10.9). When using only HBV-infection status in the parametric model and when not taking smoking, diet, alcohol, albumin or origin status into account, there was a predicted median survival time difference of 6.6 years (3).

A sub analysis excluding violent deaths (suicides, alcohol intoxication, trauma or accidental hypothermia) did not markedly alter the HR of death with HBV-infection (HR: 1.66; 95% CI: 1.10-2.51; p=0.016) (3).

As presented in table 3, we also made sub analyses on the East Greenland Inuit participants concerning survival, as HBV-infection was more prone in this group, as living conditions could differ between rural East and modern West Greenland and the probability of the same HBV genotype was higher. The crude non-parametric analysis on the East Greenlanders showed a risk ratio of 1.43 (95% CI: 1.08-1.90) for death on HBV infection status. The predicted median lifetime difference between the infected and noninfected patients was 4.5 years (0.8; 8.5), and the difference was 4.1 years when only using the HBV status in the parametric model. Finally, the adjusted Weibull-analysis showed an increased hazard ratio for infection of 1.59 (95% CI: 1.07-2.36; p=0.020) (3).

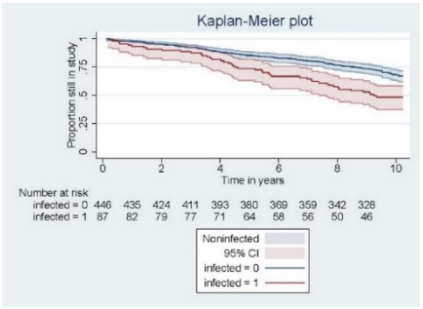


Figure 3. Kaplan-Meier plot on HBV-infection status with 95% confidence intervals and number of participants at risk during a 10-year follow-up using survival years from clinical study as analysis time.

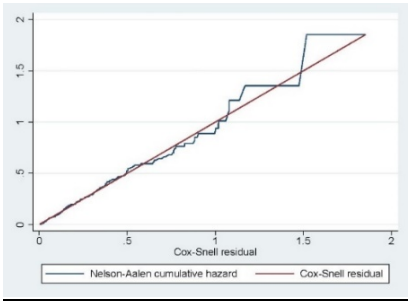


Figure 4. Cox-snell residuals against the Nelson-Aalen hazard function on model fit for the cox-model using survival years from clinical study as analysis time.

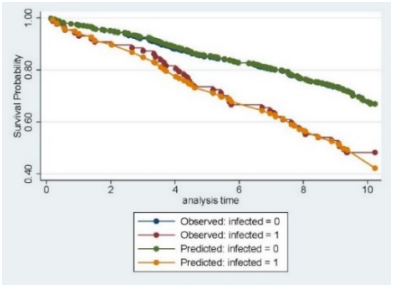


Figure 5. Kaplan-Meier observed survival curves are compared with the Cox predicted curves for Hepatitis B virus infection status. Proportional hazards assumption on infection status (infected and noninfected) depicted using survival years from clinical study as analysis time (3).

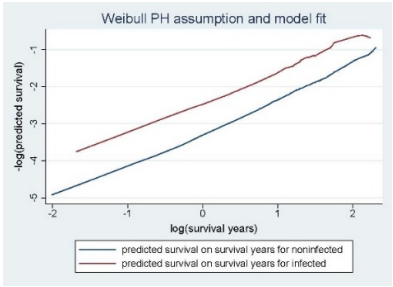


Figure 6. Visual interpretation of parametric Weibull model on proportional hazards assumption based on parallelism of lines and model fit based on linearity using age as an underlying time scale.

Elements of Denmark and Greenland

STRATEGIES USED IN GREENLAND FOR MONITORING AND CONTAINING HBV-INFECTIONS.

Unlike Alaska or Denmark, Greenland has no centralized systematic follow-up on patients with chronic HBV-infection (73,74). There is no clinical database in Greenland similar to that in Denmark, where DANHEP is a Danish Database for recording of cases of hepatitis B and C. It holds records of patients with chronic viral hepatitis admitted to hospitals in Denmark.

Notification of CHB infection to the national register of notifiable diseases is mandatory in Denmark, but reporting rates are low (74). HBV notification to the National Board of health in Greenland is also mandatory. Registration on infectious diseases show very specific numbers of Gonorrhea, Syphilis, HIV, tuberculosis and syphilis incidences from 2008 and forward. Registered HBV incidences are only shown from 2014 and forward. In total there were eight registered HBV-infections (seven in 2014 and one in 2016) (61). The mandatory notifications to the national Board of Health on HBV-infections has not been clear as there have been questions on whether both acute and chronic infections were to be notified and as a result, CHB-carriers have not been notified rigorously (correspondence with the Chief Medical Officer in Greenland). Only five cases of HBV-infections have been notified in 2017.

Hepatitis D virus (HDV) infection is not a notifiable disease in Greenland as is the case in most of the countries in the Arctic. Hence, limited information on hepatitis D infection is available (11).

A total number of 6,192 persons in Greenland have had an HBsAg blood sample analyzed in clinical practice in 2018 in Greenland. This represent 11% of the entire population in Greenland. A total of 152 were positive for HBsAg (2.5%) (data from correspondence with the Chief Medical Officer in Greenland).

It is unknown how many HBV-infected patients are followed for their infection by clinicians in Greenland. The municipality of “Qeqqata Kommunia” (population size approximately 9,400 in 2019) in the west coast of Greenland has a history of

following their HBV, HDV and HIV-infected patients (42). Records show that a total number of 480 HBV-DNA or HDV-RNA screenings or monitoring samples from Greenland have been analyzed in a period from 2010 to 2016 in Aalborg (data from supervisor Henrik Krarup [HK] in Aalborg, Denmark).

HBV diagnostics in Greenland have changed much since 1998. During the course of this PhD-study enhancements in HBV blood sampling options in Greenland have evolved to become possible to analyze in every major city in Greenland with patients from villages being able to have their HBV-infection monitored without leaving for the Capital by airplane, but by way of boat to the nearest town. Not until 2015 could HBV virology blood samples be drawn on a daily basis and shipped to laboratories abroad in general due to uncertainty in preparation. Results on analysis are still within a month delay (analyzed in Aalborg, Denmark). Results on other serological markers are with days of delay because of shipment of sera for analysis to Nuuk from any other Greenland town. Some apparatus enhancements are currently in place for PCR-analysis in Nuuk. This will shorten time for diagnosis and latency in eventual HBV-treatment.

Serological test results are not kept in the Central laboratory data file collection for more than 10 years (from correspondence with Chief biomedical laboratory technologist in Nuuk). Data extraction show a total number of 657 HBsAg positives on a period from 2007 to 2014. No earlier data on the HBV infected pregnant individuals or screenings on these (12,45) have been kept in Greenland and seem to have been lost for the moment, although data on HBV-infected individuals from Greenland have been cross-linked to social security numbers and death in earlier research done in Denmark (12). There is for that matter no follow-up on persons ever diagnosed with HBV through research. Although there have been intentions to initiate such programs, this has not been set up yet. In addition, despite that it is recommended there has been no official guidelines internally in Greenland for diagnostic work-up and follow-up, although treatment follows international and Danish guidelines.

The many different EMRs in Greenland and the limited restrictions on data management in every earlier EMR could bring any good purpose on elucidating earlier vaccination coverage, diagnosis, treatments and blood samples carried out on HBV-infected to a hold in even when evaluating on the smallest of settlements if not extremely persistent. Not to forget the unregistered newcomers or leaves with ever changing telephone numbers that only a very well informed and dedicated local health worker can grasp in settlements, while not in the urban city of Nuuk (personal report from KR on HBV and HDV infections in the village of Itilleq).

Possibilities for monitoring and treatments have been substantially improved due to the switching of the approximately 10 different EMR platforms ('Æskulap'-platforms) used nation-wide for every major city in Greenland, results from laboratory analyses (BCC-lab), guidelines, radiology scan images and descriptions (Infinnit) onto one common program platform (Cosmic) during the latest years 2014-2018 (except for east Greenland due to slow internet connection) (48). Moreover, telemedicine options have been upgraded over the decades of use (48,75,76) and more Greenlanders do become health care professionals. This improving access to health, serological-, virological-, and vaccination data on Greenlanders. Both recordings of vaccination and follow-up on CHB carriers may be optimised further as the mutual EMR (Cosmic) has been implemented more efficiently. An initial data extraction on a period from 2014 to 2018 in this system showed a total of 485 HBsAg positive samples distributed on 229 persons and with findings of 77 CHB-infected on basis of at least 2 positive samples drawn at least six months apart (data from Cosmic Information Technology-worker in Greenland).

Nation-wide guidance on HBV and HDV-infections in Greenland has been established by the author of this thesis KR and supervisor HK by easily accessible guidelines through the Greenlandic joined EMR 'Cosmic' both on screening and treating pregnant women and monitoring known HBV and HDV-infected adult patients.

Other geographical barriers to HBV-monitoring are due to the fact that most specialized work-up and apparatus is accessible only in the capital Nuuk. This include magnetic resonance cholangiopancreatography (MRCP), CT scans and liver biopsies. Biopsies are send to Denmark for evaluation and diagnosis. Ultrasonography equipment is accessible in most cities although educational skill in use differ between towns. Only one (sometimes two) radiologist are working in Greenland and only in Nuuk. No hepatologist resides in Greenland. All hepatitis infected Greenlanders in need of diagnostic work-up are referred to the consultants at the Department of Internal Medicine at Queen Ingrid's Hospital in Nuuk. Correspondence to specialists in Denmark on mail, regular "snail" mail or phone ensure updated work-up and treatment with a reliable coverage in Greenland.

Nuuk, Greenland

CHAPTER 6. DISCUSSION

Here the main results and methodological considerations of the three studies are discussed. After a brief presentation of the main results from our project, the three studies are discussed individually in relation to the current available literature. The methodological considerations are then discussed in depth and include a broad discussion of potential sources of bias and confounding, and with the addition of validity. Lastly, monitoring and containment of HBV-infections in Greenland is evaluated.

KEY RESULTS

With this project, we have documented that prevalences of serological markers of hepatitis B, D and C virus infection showed no difference between Greenlanders living in Greenland and Greenlanders who had migrated to Denmark. This imply infection before migration on an earlier age from a high endemic area to a low endemic area. Our studies did not show evidence of serological or clinical signs of disease when comparing HBV infected to non-infected when also considering alcohol consumption. Greenland Inuit had higher levels of AST, GGT and ALK than non-Inuit, regardless of alcohol intake. Intravenous drug use in Greenlanders do occur in Denmark. Survival analyses show a markedly decrease in lifespan among the HBV-infected on a 10-year follow-up, although this could not be found to be directly related to HBV-infections when looking through EMRs and registries.

STUDY 1. HEPATITIS B, D AND C ON MIGRATION.

Disease patterns may change due to migration. Based on register studies migration from Greenland to Denmark associates with higher blood pressure, obesity and some cancer forms (77–79). Some migrate due to better treatment opportunities in Denmark.

This is the first population-based comparative epidemiological investigation of viral hepatitis in Inuit populations. Median age of sexual debut in our population from Denmark showed no difference between HBV infection groups. In keeping with earlier studies, time of infection could be during childhood contacts under the age of ten, but also vertically during childbirth and sexually in adulthood (42,43). An Inuit male predominance among infected has been reported in earlier studies (12,44,49) and also on this study population (9). A more promiscuous way of living reported among younger Inuit men than women in a West Greenlandic major town may be a factor on mechanism of HBV-infection spread (50), although prevalence of HBV-infections in east Greenland resembles transmission rates throughout childhood (44,49). Distribution on markers of HBV-infection only did differ on gender with more men with markers of HBV-infection in both towns and not in the settlements in our study from Greenland. Approximately one fourth of all non-Inuit (born in low endemic Denmark) had markers of earlier infection with no gender differences. As HBV-vaccine could have been introduced to these especially while living in Denmark a sub analysis on Anti-HBc-total positivity on non-Inuit showed a difference in percentages (11% women versus 21% men) although on too few participants to make any further statistically supported conclusions. These results could relate to transmission in adulthood and therefore transmission seem possible among adults in Greenland in our study population. HBV-DNA was positive in 61 participants (87 HBsAg positive) from East and West Greenland. Three (out of the six with positive HBsAg) in Denmark had detectable HBV-DNA and 200 copies/mL being the highest. Four participants were HBsAg positive in Nuuk West Greenland and only one with detectable HBV-DNA (500 copies/ml). The highest HBV-DNA in East Greenland was 38 million copies/ml. Due to a small number of HBV-DNA positive in both Nuuk and Denmark It is uncertain whether these numbers represent differences in viral loads among Greenlanders in the areas investigated in general and a correlation to differences in age at infection. Differences in ways of spread of HBV in towns and

settlements may exist, although a full enlightenment on this aspect cannot be accounted for in this thesis.

The difference between reported hepatitis vaccinations, reported history of clinical hepatitis and actual serological markers of HBV among Inuit in Denmark might partly be due to HAV-infections and HAV-vaccinations in this population as earlier studies have shown serologic evidence and historical evidence of large epidemics in Greenland (49). Reporting of having had hepatitis in Greenland during a time period in which HAV-infections had epidemic proportion support this notion. Moreover, participants were answering yes to earlier hepatitis in remembrance of being told of having had icterus while being newborn. Also, recall bias on having had any vaccination may count for participant answering positively to having had an hepatitis vaccination.

Variations in HBV prevalence from 1.2% to 29% have been reported among Greenland Inuit (11) and may partly be related to differences in the way participants were identified and invited (1,29,45). None of the participants received antiviral therapy. The lack of clinical evidence of liver disease among the participants is in keeping with the statement in a previous publication of "a benign course of hepatitis B among adult Greenland Inuit irrespective of migration" (Rex et al. 2012, 699) (1). None of our participants had undergone treatment for HBV and none had clinical or para-clinical evidence of disease burden on investigation (1).

Co-infection of HDV in addition to HBV tends to become a more severe acute hepatitis while superinfection of HDV infection on a CHB carrier tends to become a more aggressive progression to liver cirrhosis (80). The risk of introducing HDV is a liability to Greenlanders. A concise description of the in the circumpolar region is given in the following:

"*HDV infection has been reported in 4 of 245 HBsAg-positive sera from Yukon and Northwest Territories in western Canada…while none of 186 native Indian and Inuit*

and nonnative in Newfoundland and Labrador… and none of 53 HBsAg-positive Alaskan natives had evidence of HDV infection... We found 6 anti-HDV positive in 342 HBV exposed Greenlanders in Greenland and 1 in 136 in Denmark. This is lower than the previous findings of 10% and 7% in HBsAg positive in two towns in West Greenland" (Rex et al. 2012, 699) (1,11,15,81,82).

HCV testing found non HCV-RNA positive. Our finding of two (1.5%) anti-HCV positive Greenlanders in Denmark is in concordance with results from Langer et al (29). This is also similar to reports of low prevalence in general of HCV in the remaining Arctic in the same time-period, although in urban Alaska HCV infection were more frequent and probably due to IDU (33,83).

Aalborg, Denmark

STUDY 2. LIVER FUNCTION TESTS IN THE COHORTS

Rapid development in Inuit societies (48) has been suggested to contribute to higher use of alcohol to cope with stress (84)(85–88)(89) as it has in other parts of the world (90)(91). Inuit in Denmark may consume more alcohol than their counterparts in Greenland which is plausible due to leaving Greenland with non-Inuit partners with a more regular alcohol use (92) and less binge drinking (88). Inuit may exaggerate alcohol consumption while Europeans may understate use (87). Still, underreporting in Greenland that did not take ethnic origin into account have been reported (93). Binge drinking has been a characteristic among Inuit and was accounted for in our analyses. Therefore, underreporting of alcohol use in our study is not to have been more prominent among Inuit than non-Inuit. The low number of excess drinkers in the older age groups included in our study may be related to a number of factors including high cost of alcoholic beverages in Greenland (94), a harsh environment that may cause even greater danger to the affected and select survivors due to high alcohol-related mortality rates (95) among the younger age groups (96–98). Our results show a higher alcohol consumption among non-Inuit with ”fewer abstainers and more heavy drinkers compared with Inuit” (Rex et al. 2012) and “…Higher income… and cultural differences… may explain this” (Rex et al. 2012) (92,99,100).

Inuit have Asian ancestry. As differences exist in the alcohol-metabolizing enzymes (101) across Asian ethnicities (102) this has also been suggested in Inuit (87,102) although this has not been confirmed (103). AST, GGT and ALK was higher in Inuit who never drink alcohol (2,101,104) compared to non-Inuit and Inuit ethnicity modified the association between alcohol and AST (2). Ethnic differences in LFTs between Inuit and non-Inuit Danes may exist.

Ongoing viral hepatitis infection and alcohol use may accelerate liver disease (105,106). We found no evidence of such in our study. Moreover, alcohol consumption and ongoing Hepatitis C or D virus infections may influence LFTs in Inuit, but could not be evaluated in our studies due to no cases. In addition, more

markedly elevated LFTs in clinical practice on HDV-infection has been observed in Greenland Inuit (personal recordings by KR). Moreover, liver cirrhosis is still rare among Greenlanders with HBV and HDV, although this has been confirmed on few occasions and with or without an association to a history of alcohol abuse (personal report by KR).

No systematic active immunization against HBV had been done in our cohort of participants in Greenland (9). Nevertheless, we conducted additional sub analyses on isolated anti-HBs positive individuals on other perspectives of assessment. This did not change our results.

Nuuk inland, Greenland

STUDY 3. HBV-INFECTIONS AND LONGEVITY

In this study, we reported on both life expectancy and disease occurrence among those infected with HBV, compared to biochemically confirmed noninfected individuals.

HBV-infected were likely to be older, Inuit and living in East Greenland, with a lower alcohol consumption, a more frequent use of traditional Greenlandic diet, a lower BMI and a daily smoking rate of 10-20 cigarettes. The median survival in the total surveyed cohort was 70 years (3). This is similar to the life-expectancy in Greenland that was reported at the time of the investigation (107). The predicted survival was 7 years lower for the infected individuals than for the noninfected individuals. Being infected with HBV carried a hazard ratio of 1.6 for death. This is in contrast to our findings of causes of death in the registries, as these findings suggested a lack of HBV-related deaths. As only 31% of the non-infected had died on follow up (52% for the infected), this leaves some uncertainty in the survival analyses extrapolating on basis of the known data.

Børresen et al. reported an higher IRR on all-cause death of 1.47 (95% CI: 1.21-1.79) for chronically HBV-infected persons compared to HBV-negative persons in their register study (12) in concordance to our findings. In our study IRR was 2.00 (95% CI: 1.40-2.83) for all participants from Greenland and 1.52 (95% CI: 1.02-2.26) among east Greenlandic participants.

Studying the EMRs over the 10-year period did not further indicate a burden of liver disease in this population in concordance with a number of studies that demonstrated a high prevalence of HBV among Greenlanders and a low disease burden (11). Monitoring of even inactive HBV–infected in other areas has shown to be of value, as the risk of death is still increased due to HCC in this patient group (108–110).

Aging carries a process of selection, and some early HBV infection outcomes may not be accounted for, due to the relatively advanced age of the group that was surveyed. The inclusion of this older age group is not likely to underestimate deaths that were caused by HBV infections. Two of seven registered deaths in relation to any viral hepatitis in the time period 1995 through 2013 were under 50 years of age according to the National Board of Health (37).

The diagnoses of HBV in Greenlanders may be insufficient. The expected low disease burden could result in less attention on the disease and HBV-related illnesses or deaths could be misclassified for similar reasons. There was no recording of HBV-infection in any death certificate among the participants which may support this notion (3).

Leaving Greenland was not recognized as censoring in this study and only a few participants (25 non-Inuit and 6 Inuit individuals) left Greenland during the 10-year follow-up period and events in this part of the cohort was also accounted for. Therefore, this did not influence our results or conclusions.

The medical services differed between East and West Greenland, in regard to that the main hospital in Greenland (the only hospital and therefore also the only internal medical department) is in the capital city of Nuuk in West Greenland. This difference could lead to confounding results concerning death. Moreover, socioeconomic status differ between East Greenland Inuit and Inuit in Nuuk, and further potential confounding factors on all cause death included alcohol (2), smoking (111), age, nontraditional Greenlandic food diet, ethnic origin and gender. Our data suggested an increased hazard ratio on overall death in noninfected East Greenland Inuit individuals, compared to noninfected West Greenland Inuit individuals (HR: 1.50; 95% CI: 0.93-2.41), although this result was not statistically significant (3).

Earlier studies among Greenlanders suggest alcohol consumption to be associated with accidental or violent deaths in our study population (2) and could thereby represent a potential confounding factor on infection and overall death. Moreover, alcohol and age have been suggested as being predictors of reactivation in HBV

infected, inactive carriers, and they could also be predictors of HCC and cirrhosis among HBV infected individuals (112). HBV genotype and the male gender may also be predictors of reactivation from the inactive phase (109,113). However, our data did not support these suggestions (3).

As described in chapter 2 the HBV subtype B5 is argued to be a more benign form of HBV infection. However, it associated with a higher risk of death in this cohort.

Through the EMRs and registries we identified an individual who had died from an exacerbation in hepatitis B following B cell lymphoma, in relation to chemotherapy and without a registered HBV prophylactic treatment. He was diagnosed with HBV in our clinical study and was later diagnosed within a month before his death. This emphasizes the importance of testing for HBV-infections prior to chemotherapy (114) and the importance of the availability of test results from research in clinical practice in Greenland (3).

Sisimiut, Greenland

METHODOLOGICAL CONSIDERATIONS

Strengths and limitations of the studies in this project are discussed further in the following. Systematic error, internal and external validity of the studies is also discussed in detail and evaluated.

THE CROSS-SECTIONAL DESIGNS

As all three studies in this PhD-thesis include cross-sectional designs, attention should be paid to this methodology of observational studies (115). Cross-sectional studies are valuable in being less time-consuming, less expensive than more advanced studies and can produce evidence qualifying to be a step stone to further investigation and often form the base for cohort studies. As cross-sectional studies are prevalence studies where a measured exposure and outcome is assessed at a given point in time, these measures can only be suggestive on causality of the findings, due to the limitation in establishing duration of either the exposure (in this case HBV-infection), the outcomes (clinical or paraclinical markers of disease) or both.

Cross-sectional design were used in study 1 to evaluate prevalences of HBV, HDV and HCV markers on participants in both a Greenlandic and in a Danish setting, and evaluate associations between participant characteristics, including HBV-infection status, body build and liver function tests. In study 2 the cross-sectional designs from study 1 were the basis for further investigation of associations between liver function tests, alcohol intake and HBV-infection.

THE COHORT DESIGN

In study 3 the cross-sectional study from Greenland formed the basis of a new cohort. This cohort was followed prospectively for 10 years using all available EMRs and registries from Greenland, linking results from the clinical study to evaluate all-cause mortality on HBV-infection status and to elucidate clinical aspects on the

cohort concerning hepatitis B diagnostics, cirrhosis, end stage liver disease, HCC, vaccinations and other liver diseases on participants up until 2008.

In general, cohort studies can be suggestive of the ethology or prognosis of a disease and are incidence studies (here mainly the incidence of death related to HBV-infection). In some aspects cohort studies can establish duration of either the exposure, the outcome or both, and can be used to interpret causality, although in our study exposure-time of HBV-infection is still uncertain while time until death was not.

Register studies and EMRs survey

In the cohort study (study 3) registers and EMR were used and have been discussed in short earlier, although a more detailed discussion on this matter follows. The method of linking social security numbers to participants was considered valid due to a small population.

As all available digital registries and EMRs in Greenland from the period (1998 to 2008) were used in the study, any of the reported frequencies of liver diseases, HBV-centered problems in the study are considered valid and thus resemble any known digitally registered somatic health data on the participants. In switching from pen and paper records to evolving EMRs, information might get lost. Yet, non-digitalized medical records are not used in this project and could hereby reduce the actual number of recordings on HBV-centered problems and liver problems especially on participants who had died early on follow-up and before EMRs were thoroughly established in Greenland. Although, in this time-period HBV-diagnostics in Greenland must have been (almost) inaccessible in clinical practice and, registry of HBV-related problems with pen and paper is considered minimal. The EMR reported number of HBV-related diagnostics are considered as approximately the actual number of clinical findings due to the mandatory journaling /recordkeeping in Greenland and therefore if anything then an underreporting of findings. As described under the results-section HBV-diagnostics or even vaccination recordings in a clinical

setting seem rare in Greenland. Unfortunately, a comparison of EMR findings and recordings of laboratory analyses could not be directly assessed as the earliest digital laboratory recordings were not established until 2007.

The data collectors in the clinical study were blinded to the HBV status of the participants. The data collector investigating the registries was not blinded to the HBV-infected, but estimated to have very little impact on the data collection, as similar procedures were used for all of the participants, and all of the available data were scrutinized for information of HBV and liver disease relevance (3).

Registers have inherent limitations on diagnosis and on causes of death, and there are no statements of uncertainty in the Danish Death Registry although, diagnosis on biopsies from the Danish Biopsy Registry is considered as the gold standard on verifying diagnosis. Death registry diagnosis on HBV-infections and on HCC on Greenlanders is considered to be less than actual incidences, as the liver is a site of metastasis and because autopsies are not regularly done on Greenlanders in Greenland unless considered unnatural (forensic autopsies with staff coming in from Denmark). Moreover, although death certificates are mandatory in Denmark and Greenland evaluation on death causes on the certificates done at a hospital are usually performed by (busy) physicians on shifts, with minor prior knowledge on the person who had died. This leaves some uncertainty in death certificate diagnosis. At least one participant in our study had a discordance with a liver biopsy verified as HCC and a death certificate diagnosis with lung cancer being the official death cause without the mentioning of liver cancer.

Qaqortoq, Greenland

Nuuk, Greenland

SYSTEMATIC ERROR

Selection Bias

Selection bias involves biases arising from the procedures by which the study participants are selected from its source population, or select themselves by agreeing to participate. Thus, selection bias is the introduction of a systematic difference in the selection of participants from factors that influence study participation. Selection bias can occur if the studied population does not reflect the population from which it is derived from and therefore be introduced into the included studies if the participants differed from the non-attenders. A randomized selection of potential participants and a high participation rate reduces the introduction of selection bias. As a randomized selection was achieved in West Greenland this minimizes the risk of selection bias here. East Greenlandic participants were not randomized as all in the selected age groups were invited, but

as 96% of all invited East Greenlanders participated the introduction of this form of bias is negligible, as the cohort comprises the overall of the entire source population. Also, as markers of HBV might accumulate in an aging part of the population the selection of only elderly participants in a population might overestimate the overall prevalences of the whole population. Differences in recruitment of participants existed between Denmark and in Greenland. As described the potential participants in Nuuk had initially been selected using the hospital registration system in Nuuk in 1998 and later validated by comparing the list to the National Civil Registration System (NCRS). Of the 480 persons initially selected (25% of all 1920 persons in the selected agegroup in Nuuk in 1998) a total of 255 persons had moved or died and therefore could not be contacted on the registered address and therefore found not eligible for the study. In East Greenland the NCRS was used in both the settlements and in the town and only 9 persons out of 161 potential participants from the settlements and 13 out of 197 potential participants from the town were not eligible due to latency in reporting of death or changing of addresses. Therefore, the initial selection in Nuuk did pronouncedly differ from the final selection leaving some uncertainty to whether the selected group could differ in composition to the background population in Nuuk and also in HBV-infection arrangement. Hereby, selection bias could have been introduced to the participants in Nuuk. Whether the potential selection bias here would increase or decrease the prevalence of HBV-infected in Nuuk or the health statuses on HBV disease is uncertain when the knowledge on this part of the population (Greenlanders with frequent changing of addresses within a town, not managing to officially change addresses, leaving for other towns in Greenland or Denmark as an example) is also uncertain. This part of the population could be of opposites in matters of HBV-infection composites, although no proof lies on behalf of that HBV-infected in Greenland should be more prominent in marginalized groups or in any specified social group. The overall assessment is that it might not entangle with the overall findings from Greenland leaving little selection bias.

For the recruitment of participants in Denmark small differences are apparent. Only individuals born in Greenland with at least one parent born in Greenland were included and with the supplement of Greenlanders aged 40 through 49 years also invited. As in East Greenland everyone with the inclusion criteria were to be invited. The initial contact by telephone on behalf of the inclusion criteria for most participants in Denmark also differed from the recruitment from Greenland. Eligibility of the 92 subjects who did not respond in Denmark is uncertain. Whether HBV or HCV status for that matter differs in this group introducing bias by invitation is uncertain. Marginalized Greenlandic groups in Denmark without addresses or telephones might have higher prevalences of viral or bacterial infections, although this group count for very few but visible individuals in a mostly Caucasian population. A greater part might not have responded due to not having any affiliations to Greenland neither ethnically, familiarly or in recollection of ever living there or as in Greenland: because of frequent migration between towns. Bias by invitation on HBV-status on this behalf is therefore estimated to be small on the participants from Denmark.

Other possible selection bias problematics is the time difference on which the two cross-sectional studies were performed, and also the age differences among participants.

The age group in Denmark also included 40 to 49 year olds. There were no internal statistical differences on behalf of HBV-exposure, drinking habits or BMI, although there was on gender, when comparing two groups of age intervals 40 through 49 and 50 through 69. The results section primarily contain age groups 50 through 69 for direct logical comparison when comparing Greenlanders in Denmark and in Greenland, although there was no statistical proof of differences if all participants from Denmark were included. Moreover, when comparing age in the two cross sectional studies the age of the youngest participant in Denmark if examined in 1998 would have been 32 years. As age at infection might be before this age on most in

the Greenlandic population the inclusion of the younger age groups are not to bias the result on HBV-status markedly and should be comparable to the participants living in Greenland, although small time trends may exist in general concerning child delivery, kindergarden opportunities and sexual behavior (46,48,50). As described in the results section HBV-status on participants living in Denmark mirrored the participants living in Greenland.

As described in the results section having both parents born in Greenland increased the risk of having had an HBV-infection among Greenlanders in Denmark. Also, only a selected greater group of Greenlanders migrate to Denmark. Out of 136 participants in Denmark 25 had only one parent born in Greenland. Only three had a mother born outside Greenland (on the risk of vertical transmission if mother is infected). Of a total of 441 Inuit in Greenland, seven participants had only one parent born in Greenland and none had a mother born outside Greenland. A potential source of selection bias lies herein. This on behalf of ethnicity (on the measure of parents born in Greenland) and migration on HBV-infection. This could lead to a reduction in overall prevalences of HBV-exposure in Inuit found in Denmark in direct comparisons with prevalences in Inuit in Greenland due to differences in composition of parent's birthplace, although this was not found in our cross-sectional studies. This might apply if the real composition of Inuit in the age groups investigated in Denmark comprise of more individuals with mixed parents than actually investigated and thus bias our findings away from the null when comparing prevalences of HBV-markers between Inuit in Denmark and in Greenland.

Sisimiut, Greenland

Information bias

Information bias is the result of misclassification of study participants with respect to disease or exposure status. Thus, the concept of information bias refers to those people actually included in the study. The misclassification can be either non-differential (random error) or differential (116).

Inuit ancestry was defined in this project as of being born in Greenland and having had at least one parent born in Greenland. The selection (Inuit in Denmark) or division of participants on behalf of Inuit ancestry was primarily broad into the equation in a way to try and consider if a genetic aspect (particular genetic constitution) derived from the Neo-Eskimo (117) could explain some of the benign outcomes of HBV disease found in earlier studies. Participant parents born in Greenland were born while the country was highly secluded. A misclassification of Inuit ancestry is therefore evaluated to be very small, and count for one or two subjects (false negative) included in the study.

All data collections were at one point in time. Reported dietary habits, smoking habits and alcohol use were variables used in the different studies. The questionnaire on these subjects were clearly defined, the same interpreter was used in Greenland on all participants and the questions were asked as they were written in the questionnaire. This minimized the risk of differences caused by translation and interview technics. Recall bias is a type of information bias. The intra-individual variability of predictors has not been taken into account in the survival analyses and moreover, misclassification of place of living on all participants both in villages, towns and cities may exist on follow up due to migration. As an example on aging, people may migrate to the towns from villages or move to Denmark (has been accounted for and discussed) for better living conditions. The migration to towns seem to affect very few individuals on follow up.

Misclassification on alcohol intake has been discussed earlier on aspects of ethnicity. In addition, gender differences in reporting could exist and the reporting of alcohol intake could differ between Inuit in Greenland and on Inuit migrants. As all Inuit were born in Greenland with the same overall cultural setting, the misclassification on alcohol use due to migration is considered non-differential. A difference in reporting of alcohol between genders according to ethnicity could exist and could be differential (differential misclassification) and be postulated to be greater among non-Inuit due to cultural differences, but this will not hamper our results, as these problematics are not incorporated in our analyses due to stratification on gender (only sub analyses using men in the results section). Underreporting of alcohol use may differ according to alcohol intake groups, and could also be differential or non-differential between genders and ethnic groups. Moreover, all blood samples drawn were immediately separated and frozen for storage and analyses were done in random order. Storage duration was approximately the same for all samples. Misclassification due reports on habits, storage time and laboratory analyses on blood samples are considered non-differential.

As HBV-infection markers were only measured on one occasion on all participants, misclassification of chronic and acute infections could be evident, although this misclassification is considered to be of a very small size. Also, non-infected individuals could become infected or clear an infection during a course of ten years. Both scenarios are considered to potentially count for very few subjects and not bias the results markedly.

The diagnostic classifications on HBV-exposure has been described in the methods section and the unorthodox assessment of earlier infection based on Anti-HBs alone has been discussed in earlier studies (9,118) an briefly under study 2. Sub analyses did not change with selecting this group as of being vaccinated against HBV-infection. Nonetheless, study 3 shows that looking through the EMRs one participant was recorded as of being HBV vaccinated by 2008. This person was non-Inuit. This

cross-validates the assumption of no earlier vaccination among the Greenland Inuit in the investigated period. Thirty Inuit from Greenland and five non-Inuit were found isolated anti-HBs positive in our cross-sectional study in Greenland. Misclassification could still exist especially among the last four non-Inuit and be of minor importance.

The validity of accuracy in the analysis of Hepatitis serology is considered very precise, although specific validities on this aspect is not part of the PhD-project. Misclassification is considered very small.

Misclassification of ill participants with serious disease due to HBV-infection (compensated liver cirrhosis or HCC) into a category of healthy persons in the clinical studies is possible with the options used. No diagnostics on imaging or liver biopsies were used in the clinical studies, although these methods of diagnostics were incorporated into Study 3. Transient elastography has yet to be introduced in Greenland. As HBV-virus infections were not in focus in the clinical setting when going through EMRs and as same methods were used in going through all records, the misclassification on these aspects are evaluated to be non-differential and in any case bias the results towards the null. As blood samples were frozen for transportation analysis on alanine aminotransferase (ALT) was not carried out. Due to instability in results AST was used instead. As ALT is the most common liver enzyme used in judging eventual hepatitis B flairs it is unfortunate not to be able to use this parameter when other LFTs were available. Subsequent ALTs were tried analyzed but could not be accomplished (a personal report by SA).

Misclassification of the causes of death in the registries was possible if the nondiagnosed HBV-infected individuals died of undetected, HBV-related diseases. This problematic is described in detail above.

Nuuk fjords, Greenland

Confounding

Confounding occurs when the exposed and non-exposed have different background disease risks (115,116). Confounding can be controlled for in observational studies by the study design in terms of restriction and/or by either stratification or multivariable techniques on analyses. The adjustment for potential confounders can be sufficient, insufficient or overestimated and may bias associations (116,119). Restrictions by design were the inclusion criteria with specific age groups, specific areas of investigation and the ability to make an informed consent. In order to diminish confounding stratification of data, multivariate linear and logistic regression models, adjusted cox and parametric survival analyses were used to test associations between exposures and outcomes. Specific analyses are described in detail in the methods section.

Leaving out adjustment may lead to residual confounding (120). Unmeasured confounding cannot be adjusted for (119) and some degree of residual confounding (stratification of the confounder is not fine enough or confounding exists within strata) is likely to persist. The categorization into alcohol group may introduce residual confounding. No data was generally available on physical activity, intake of sugars, age at first intercourse, socio-economic factors such as education level and employment status, which could be suggested to be confounders and effect modifiers on either liver biochemistry, HBV-distribution or death. Educational level and sexual debut was only incorporated into the study in Denmark.

EFFECT MODIFICATION

Effect modification means that the effect of the exposure depends on the level of another variable. Effect modification shows a phenomenon that may have biological, clinical or public health relevance (119). Assessment on this has been presented in the statistics section on used on multivariate analyses. On note, as no non-Inuit had an ongoing infection in our studies, a measure of an interaction between ethnicity and infection could not be assessed(also addressed earlier).

CHANCE

Throughout this thesis results of the investigations have been presented with focus mainly based on clinical concerns and knowledge, and statistical associations have also been discussed in this manner (71,119,121). Stronger statistical associations and minimizing random error could be possible with increased sample size (116) as error due to chance decreases as sample size increases (116). On the aspect of chance, the main findings have been consistent in relation to other studies made on HBV-infected in Greenland.

VALIDITY

On basis of what has been discussed in the previous sections the internal validity of the studies among Greenlanders in Greenland is considered very high. The internal validity or comparability of Inuit in Denmark and Greenland in general on infection status may be questioned as they differed partially on gender, age, ethnic origin and time of investigation. These considerations have been answered in the previous section and comparability is judged adequate. In addition, the gender distribution differences between Inuit women in Denmark and in Greenland in our studies mirror the male predominance among non-Inuit in Greenland as they couple on leaving Greenland for Denmark.

Our definition of Inuit may not apply in future studies on younger generations. This due to the admixture of other ethnicities and as more ethnic Greenlanders are born abroad (especially in Denmark).

With the very low prevalences of HIV, HCV, HDV and also alcohol abuse, this project gives an exceptional insight into the features of the HBV-mono-infections found in Greenland without the confounding of host characteristics. Although the sample sizes of the cohorts in this project are small our findings are judged applicable to the Greenlandic population in general in present also in extrapolating to other age groups. Our project could also give some insight to the course of infection among other Inuit and native groups in the circumpolar regions and beyond.

A DISCUSSION ON MONITORING AND CONTAINING OF HBV-INFECTIONS IN GREENLAND

As no nationwide HBV-monitoring program exists the actual number of infected has not been accounted for and is therefore very uncertain. According to earlier research done on Greenlanders the prevalence of HBV-infected varies from 1.2 to 29% of the population and the actual number of HBV-infected could count for up to four

thousands. The actual number of HBV-patients monitored may account for a few percentages of the overall infected in Greenland.

A general characteristic among Greenland Inuit has been the lack of apparent disease among those infected with HBV. Hence, there has been little attention to the need for treatment of HBV infected in Greenland.

Even though HBV is a notifiable disease in Greenland, this is seldom done. The extremely low notification of HBV by medical health workers can be based on very little knowledge on this mandatory setup or difficulties in time to serologic diagnostic test results. Difficulties in interpretation of HBV serological results for the untrained eye is also an option as HBV diagnostic interpretation is not a skill that is usually taken into account when chosen for medical work in a city with surrounding villages in Greenland. The main medical doctor work force in Greenland are broadly specialized with mostly a background in General Medicine, although a major part of the medical work force also contain short term Scandinavian locum tenens physicians and surgeons who not necessarily know about HBV-infections in Greenland. Also, daily disease focus is elsewhere in the broad medical departments where other acute illnesses way overpass focus from chronic diseases like HBV. Anyhow, the resolve to further diagnosing HBV status of Greenlanders is undoubtedly lacking and could also be an active decision from the medical clinician due to lack of resources and presumable low disease burden or on the thought that notification has already been done prior or due to unclear guidelines. A simplified way to register notifiable diseases may heighten compliance also taking into account easily accessible ways to diagnose diseases and also raise awareness of registration.

Better education among patients and the health care personnel including public health care nurses (‘Sundhedsplejersker’) is essential. Also, greater public awareness is necessary if problems are to be solved. Very few problems in Greenland like HBV-infections can be isolated to one specific cause only and problems HBV alike are to be solved differently in a diverse country as Greenland. Solving infectious disease

problems in Greenland generally speaking is only possible if economic and social issues (poverty) are also addressed (122).

As addressed in the results section (monitoring and containment) HBsAg-positivity in the general population still occur. Monitoring people with an infection on which we have very little evidence of disease burden, could have a stigmatizing result especially from health personnel and others with no prior knowledge to the nature of HBV-infections in Greenland, yet without known benefits for the patient. A discussed earlier there is no evidence that the HBV-infected in general in Greenland should be a more resource weak or marginalized group. On this statement, people with HBV-infection in Greenland could also have the same basic compliance as any other Greenlander. Anyhow, monitoring of the HBV disease will lead to better understanding of the disease in Greenland, better patient effort, which again will lead to more economic considerations in a country with fewer resources than countries we compare us to (46,48). One should take into account that the number of HBV-infected in Greenland far exceeds the number of any other notifiable disease all put together. The matching of expectations on distribution of resources to a monitoring program of HBV-infected should also be kept in mind on implementation. A feasible way of monitoring (48,72) or at least diagnosing HBV in Greenland could be using the joint EMR making viral hepatitis B a general diagnostic option. A monitoring program should derive on indicators found as important in other monitoring programs although the monitoring platform should be a part of the joint EMR, otherwise the risk of not using the platform will be evident. An effort should be put into analysis of effectivity and feasibility on the desired monitoring program (48). The linkage between para-clinical evidence of a Hepatitis B infection or CHB should in essence be coupled to the EMR automatically without need for manual entry, faulty registry and unnecessary delays although, overall assessment should be done by specialists.

Also, as the turnover of medical staff is very high in Greenland leaving holes in continuity in also patient disease monitoring and as this does not seem to be solved in the near future, no doubt leaving more influence on patient inclusion in own treatment and monitoring is a great part of the monitoring options in the future.

Only a few HBV-infected patients have been identified with signs of moderate fibrosis on liver biopsy in Greenland. These patients were treated with lamivudine and later with tenofovir. Only very few patients with HDV-infection have been treated in Greenland with interferon-alpha or pegylated interferon. This partly due to side effects and living in remote areas embodying the very essence of issues that may arise in the Greenland health care system. Also, systematic follow-up on these patients has not been fully undertaken yet (11). Moreover, common anti-viral drugs against HBV (and HCV) used in Greenland do seem to fall in price (123).
HDV-infection continues to be a problem in Greenland as superinfection in chronic carriers of HBV has caused severe liver disease even in children. An outbreak of hepatitis D infection was reported in one settlement in West Greenland (45), but also sporadic cases have been identified from the remaining parts of the west coast. The very high number of Inuit with HBV infection in Greenland and the other Arctic countries poses a risk to the Inuit societies if HDV escalates the age groups with horizontal spread (11).

Threat of horizontal spread of HIV and Syphilis among sexually active younger age groups and also in pregnant women has shifted to become an actual problem during the latest years in Greenland (2017-2019). The attempt to lessen sexual transmitted diseases is ongoing in Greenland. Greenland reports the highest rates of infection with chlamydia and gonorrhea in the North American Arctic (124) . HCV has not reached epidemic proportions as only very few are diagnosed every year. Intravenous drug use is still not an issue in Greenland. HBV-transmission is theoretically possible due to virus in body fluids such as breastmilk (125,126), salvia (127), tears (128), semen (129), vaginal secretion (130) , urine (131) or through

contaminated blood and products or infected needles. HBV may cause disease transmission from objects even if dried for a week or maybe even longer (132). HBV could still be an active virus though heated to 69 degrees Celsius for 10 hours (133). Horizontal transmission of disease is therefore an issue on household contacts, between children at day-care centers (134) and sexually. Vertical infections with HBV are mainly transmitted in uterus through the placenta from the maternal blood to the fetus of infected mothers although infections through vagina or oocytes is possible (130).

Due to better accommodations in Nuuk compared to many other towns and villages in Greenland the risk of getting the virus during early childhood might be relatively small, although the capital is growing rapidly with migration from higher endemic areas of Greenland and with the undeclared nurseries, daycares and kindergartens evolving due to a huge demand which cannot be upheld by the municipality.

The active HBV immunization coverage rate among newborns was only 55% and only 38.5% had received the fourth hepatitis vaccination in Greenland in 2012. Fortunately, a newer study using the joint EMR: 'Cosmic' showed a 98.7% coverage on HBV-vaccinations among newborns, but only 69.8% received the fourth vaccination in Nuuk in 2015 through 2016, although the nationwide coverage was still unknown. An estimate of newborn HBV vaccinations in Nuuk in 2016 including children born outside Greenland showed a coverage of 94%, while it was 76% for the 2nd vaccine (at 3 months), 75% for the 5 months vaccine (3rd vaccine offered in the childhood vaccination program) and 63% for the 12 months (4th) vaccine (135). This still gives an opportunity for HBV to spread among the youngest and adolescents although the childhood vaccination program undeniably leaves a huge step stone in containing the HBV spread.

Combining the health care efforts in general will give a more robust handling against transmission of the HBV. A monitoring program both on HBV-infected and on HBV-

vaccinations is to be simple and robust, so that a pause in the program (regionally) can easily be picked up and continued later. Monitoring HBV in Greenland could become a landmark in monitoring infectious diseases and other liver diseases in Greenland. Monitoring other diseases through methods alike could align and follow.

Grocery shopping in Nuuk and in a settlement

Differences in housing conditions in Greenland

CHAPTER 7. PERSPECTIVE AND FUTURE STUDIES

This project shows that HBV-infection is an important factor on survival on Greenlanders and that studies should aim at confirming and explaining our findings. Also, our project should be followed-up. The preliminary results of a 10-year follow up on the Greenlandic cohort is in compilation and a twenty-year follow up is on the way. Although both studies lie beyond this PhD-study it seems as preliminary results from the 10-year clinical follow up look as if disease burden is low.

Through our studies monitoring of disease have not been directly achievable until now. A letter to participants with HBV-infections should be send offering them the possibility to be monitored as HBV-patients in clinical practice as this possibility has emerged in Greenland in the years after the cross-sectional study in Greenland. Information to health care centers in Greenland should be send (again) on the infected to inform them on the implementation of follow-up. This will in turn give better understanding of the disease, to insure treatment on indication and to reduce risk of cirrhosis, end stage liver disease and HCC.

Nonetheless, follow up is required for a better understanding of the HBV infection among Greenlanders and studies that as an example examine vaccination serology in Greenlandic children on childhood vaccination would give further insight to containment of the infection.

Other scientific model designs could be useful to give further insight into HBV-infections in Greenland, but knowledge into the natural course of HBV-infections in Greenland should be attainable through proper monitoring in clinical practice on this widespread viral disease.

CHAPTER 8. CONCLUSIONS AND RECOMMENDATIONS

Through the studies included in this thesis we have enlightened aspects on HBV-disease in Greenland and among Inuit migrants in Denmark. We document that HBV-, HDV- and HCV-infection marker proportions in Denmark Inuit mirror proportions reported in Greenland and imply infection on Greenland Inuit before migration on an earlier age from a high endemic area to a low endemic area. We find evidence in our study population of the possibility of HBV-infections to be transmitted in adulthood in addition to infection transmission earlier in life. Our study show that intravenous drug use can be introduced to (few) Greenlanders on migration and therefore this way of introducing blood borne infections to Greenland Inuit exists. There is no evidence of elevated LFTs in Inuit on HBV-infection in the cross-sectional studies presented when measuring AST, bilirubin, ALK, GGT or albumin and no evidence of illness on clinical assessment nor on body build parameters. This is in full compliance with earlier observational studies performed in Greenland. Our project shows that LFT values (AST, GGT and ALK) are generally on a higher level in Greenland Inuit than in non-Inuit regardless of alcohol intake. Moreover, the association between alcohol intake and AST was modified by ethnic origin with higher levels of AST among Inuit than on non-Inuit on the increase of alcohol use. This suggests ethnic differences in liver biochemistry irrespective of alcohol consumption. In contrast to our other findings Inuit with HBV-infection have a profound reduced lifespan on a 10-year follow up, although no direct relation to severe liver disease due to HBV-infection could be found when looking into data registries and EMRs. The increased mortality on HBV-infection is in concordance with earlier register studies performed on Greenlanders.

In a clinical setting, matters on HBV-infections have lost their momentum in Greenland with the risk of undiagnosed HBV-related deaths. In no opposition to many other health issues, obstacles still lie ahead concerning HBV-infection in a small

population on a vast island with scattered cities and settlements which are only accessible through air or water. Education, social problems and poor accommodations are serious issues that are also important to look into when trying to eliminate the HBV-infections in Greenland. This must be considered on a public scale when dealing with also other infectious disease problems. The development in Greenland in general leaves great enhancement opportunities for also HBV-monitoring of which some are being used. Monitoring and treatment opportunities for HBV-infected have substantially improved due to unifying the electronic medical records and guidelines, improving access to health, serological- and virological data on Greenlanders. The accessibility to blood sampling has also improved the HBV-diagnostics. Extraction of data from the EMR could be a feasible way to monitor HBV-infected in Greenland, although regional differences must apply on specific matters on HBV-monitoring for a more effective setup. A feasible way of getting a clinical database on HBV-infected Greenlanders and on status of HBV-exposure is to reach out centrally in Greenland and propose to get all available data on infection status. This by gathering information from all the different Health Centers in the towns of Greenland, from "Statens Serum Institute" (SSI) in Denmark, from the Aalborg University hospital in Denmark and, through data done on research on Greenlanders over the years. Management should also rely on diagnosis by a yearly extraction of HBV-serology from the nationwide laboratory findings (BCC-lab) combined with establishing a generally attainable specific HBV-diagnosis code in the joint EMR (Cosmic). Combining knowledge on and methods of work-up with other chronic disease monitoring programs such as the diabetes program in Greenland, this could increase patient compliance and education of patients and health workers on matters of HBV-infections in the different regions of Greenland. HBV-infection tracing should be committed to the local health workers managing sexual transmitted diseases, public health care nurses ('sundhedsplejersker') or others health care services that also embody vaccination strategies in the different regions in Greenland. The attempt to lessen sexual transmitted disease is ongoing in

Greenland. Horizontal spread of disease other than sexually must also still be in focus. Hygiene in limiting infections and high quality kindergarten accommodations must be emphasized. Leaving more influence on patient inclusion in own treatment and monitoring is a great part of the monitoring options in the future. Better education to patients and healthcare workers is therefore extremely important. Education on matters of HBV-infections should be ongoing to keep momentum. The way to register notifiable diseases should be clarified and simplified and educational tools in the Greenlandic native language and dialects (especially East Greenlandic) should all be accessible through the EMR for both patients and health personnel. Nationwide communication directly to disease-managing medical doctors in the capital either by phone or by interactive media will leave better opportunities for education and HBV-testing, vaccinations and monitoring. The very high turnover on medical staff in Greenland that can leave holes in continuity on patient disease monitoring locally may be bypassed in doing so. The group with CHB is of considerable size and co-infection or superinfection with HDV can turn into a general serious problem if horizontal spread escalates. CHB poses a risk to the society of Greenland. HBV-vaccines to all non-exposed Greenlanders and to immigrants and monitoring of the HBV-infected will be an effective way to lessen the HBV-related problems in the future.

Sled dogs resting after a long trip, Sisimiut, Greenland

REFERENCES

1. Rex KF, Krarup HB, Laurberg P, Andersen S. Population-based comparative epidemiological survey of hepatitis B, D, and C among Inuit migrated to Denmark and in high endemic Greenland. Scand J Gastroenterol. 2012;47(6):692–701.

2. Rex KF, Krarup HB, Laurberg P, Andersen S. Liver biochemistry and associations with alcohol intake, hepatitis B virus infection and Inuit ethnicity: A population-based comparative epidemiological survey in Greenland and Denmark. Int J Circumpolar Health. 2016;75:1–12.

3. Rex KF, Krarup HB, Pedersen ML, Andersen S. Reduced life span with chronic hepatitis B virus infection – a 10-year follow-up study in Greenland. Submitted. 2019;(February):21.

4. World Health Organization. Global hepatitis report, 2017. WHO. 2017. 1-68 p.

5. WHO Hepatitis B [Internet]. [cited 2018 Oct 18]. Available from: http://www.who.int/news-room/fact-sheets/detail/hepatitis-b

6. Storm HH, Nielsen NH. Cancer of the digestive system in Circumpolar Inuit. Acta Oncol (Madr). 1996;35(5):553–70.

7. Xu C, Zhou W, Wang Y, Qiao L. Hepatitis B virus-induced hepatocellular carcinoma. Cancer Lett [Internet]. 2014 Apr 10 [cited 2018 Nov 14];345(2):216–22. Available from: https://sfx.aub.aau.dk/sfxaub?ctx_enc=info%3Aofi%2Fenc%3AUTF-8&ctx_tim=2018-11-14T16%3A22%3A32IST&ctx_ver=Z39.88-2004&frbrversion=6&req.language=dan&rfr_id=info%3Asid%2Fprimo.exlibrisgroup.com%3Aprimo3-Article-sciversesciencedirect_elsevier&rft.artnum=&rf

8. McMahon BJ. The influence of hepatitis B virus genotype and subgenotype on the natural history of chronic hepatitis B. Hepatol Int [Internet]. 2009 Jun 26 [cited 2018 Oct 24];3(2):334–42. Available from: http://link.springer.com/10.1007/s12072-008-9112-z

9. Krarup HB, Andersen S, Madsen PH, Okkels H, Hvingel BH, Laurberg P. Benign course of long-standing hepatitis B virus infection among Greenland Inuit? Scand J Gastroenterol. 2008;43(3):334–43.

10. Andersen S, Hvingel B, Kleinschmidt K, Jørgensen T, Laurberg P. Changes in iodine excretion in

50-69-y-old denizens of an Arctic society in transition and iodine excretion as a biomarker of the frequency of consumption of traditional inuit foods. Am J Clin Nutr [Internet]. 2005 Mar 1 [cited 2019 Feb 10];81(3):656–63. Available from: https://academic.oup.com/ajcn/article/81/3/656/4649026

11. Rex KF, Andersen S, Krarup HB. Hepatitis B among Inuit: A review with focus on Greenland Inuit. World J Hepatol [Internet]. 2015 May 28 [cited 2018 Jul 26];7(9):1265–71. Available from: https://sfx.aub.aau.dk/sfxaub?ctx_enc=info%3Aofi%2Fenc%3AUTF-8&ctx_tim=2018-07-26T14%3A30%3A31IST&ctx_ver=Z39.88-2004&frbrversion=2&req.language=dan&rfr_id=info%3Asid%2Fprimo.exlibrisgroup.com%3Aprimo3-Article-medline&rft.artnum=&rft.atitle=Hepatitis+B+am

12. Børresen ML, Koch A, Biggar RJ, Andersson M, Wohlfahrt J, Ladefoged K, et al. Hepatocellular carcinoma and other liver disease among greenlanders chronically infected with hepatitis B Virus: A population-based study. J Natl Cancer Inst. 2011;103(22):1676–85.

13. Minuk GY, Macrury S, Uhanova J, Caouette S, Coleman N, Cummings K, et al. A paucity of liver disease in Canadian Inuit with chronic hepatitis B virus, subgenotype B6 infection. J Viral Hepat. 2013;

14. Kowalec K, Minuk GY, Børresen ML, Koch A, McMahon BJ, Simons B, et al. Genetic diversity of hepatitis B virus genotypes B6, D and F among circumpolar indigenous individuals. J Viral Hepat. 2013;

15. Harpaz R, McMahon BJ, Margolis HS, Shapiro CN, Havron D, Carpenter G, et al. Elimination of New Chronic Hepatitis B Virus Infections: Results of the Alaska Immunization Program. J Infect Dis [Internet]. 2000 Feb 1 [cited 2019 Mar 4];181(2):413–8. Available from: https://academic.oup.com/jid/article-lookup/doi/10.1086/315259

16. Chang MH, Chen CJ, Lai MS, Hsu HM, Wu TC, Kong MS, et al. Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. Taiwan Childhood Hepatoma Study Group. N Engl J Med. 1997;

17. Baruch Blumberg, MD, DPhil » Hepatitis B Foundation [Internet]. [cited 2018 Oct 18]. Available from: http://www.hepb.org/about-us/baruch-blumberg-md-dphil/

18. Hepatitis B Virus Infection — Natural History and Clinical Consequences. N Engl J Med [Internet]. 2004 Sep 16 [cited 2018 Oct 18];351(12):1268–1268. Available from:

https://sfx.aub.aau.dk/sfxaub?ctx_enc=info%3Aofi%2Fenc%3AUTF-8&ctx_tim=2018-10-18T17%3A07%3A38IST&ctx_ver=Z39.88-2004&frbrversion=2&req.language=dan&rfr_id=info%3Asid%2Fprimo.exlibrisgroup.com%3Aprimo3-Article-nejm&rft.artnum=&rft.atitle=Hepatitis+B+Virus+Infection+—+Natural+History+and+Clinical+Consequences&rft.au=&rft.aucorp=&rft.auinit=&rft.auinit1=&rft.auinitm=&rft.aulast=&rft.ausuffix=&rft.btitle=&rft.coden=&rft.date=2004-09-16&rft.eisbn=&rft.eissn=1533-4406&rft.epage=1268&rft.genre=article&rft.isbn=&rft.issn=0028-4793&rft.issue=12&rft.jtitle=The+New+England+Journal+of+Medicine&rft.object_id=&rft.pages=1268-1268&rft.part=&rft.quarter=&rft.sici=&rft.spage=1268&rft.ssn=&rft.volume=351&rft_dat=%3Cnejm%3E10.1056%2FNEJM200409163511228%3C%2Fnejm%3E%3Cgrp_id%3E8934468553429553071%3C%2Fgrp_id%3E%3Coa%3E%3C%2Foa%3E%3Curl%3E%3C%2Furl%3E&rft_id=info%3Adoi%2F10.1056%2FNEJM200409163511228&rft_id=info%3Aoai%2F%3E&rft_id=info%3Apmid%2F&rft_pqid=&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&svc.fulltext=yes&svc.holdings=yes&svc_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Asch_svc&url_ctx_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Actx&url_ver=Z39.88-2004&vid=main

19. Feitelson MA, Clayton MM, Blumberg BS. X antigen/antibody markers in hepadnavirus infections. Gastroenterology [Internet]. 1990 Apr 1 [cited 2018 Oct 26];98(4):1071–8. Available from: http://linkinghub.elsevier.com/retrieve/pii/001650859090035Y

20. F.Ramalho, G.Carvalho, F.Bonino*, J.Velosa, A.Silva, A.Batista MC, Moura D. Hepatitis B core antigen in hepatocytes from liver biopsies of patients with chronic hepatitis B virus (HBV) infection: Correlation with serum HBV-DNA and liver histology. J Hepatol [Internet]. 1986 Jan [cited 2018 Nov 8];3:S155. Available from: https://sfx.aub.aau.dk/sfxaub?ctx_enc=info%3Aofi%2Fenc%3AUTF-8&ctx_tim=2018-11-08T17%3A39%3A41IST&ctx_ver=Z39.88-2004&frbrversion=2&req.language=dan&rfr_id=info%3Asid%2Fprimo.exlibrisgroup.com%3Aprimo3-Article-sciversesciencedirect_elsevier&rft.artnum=&rf

21. Terrault NA, Lok ASF, McMahon BJ, Chang K-M, Hwang JP, Jonas MM, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology [Internet]. 2018 Apr 1 [cited 2018 Nov 8];67(4):1560–99. Available from: http://doi.wiley.com/10.1002/hep.29800

22. Lampertico P, Agarwal K, Berg T, Buti M, Janssen HLA, Papatheodoridis G, et al. EASL 2017

Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol [Internet]. 2017 Aug [cited 2018 Jul 27];67(2):370–98. Available from: https://sfx.aub.aau.dk/sfxaub?ctx_enc=info%3Aofi%2Fenc%3AUTF-8&ctx_tim=2018-07-27T17%3A16%3A55IST&ctx_ver=Z39.88-2004&frbrversion=2&req.language=dan&rfr_id=info%3Asid%2Fprimo.exlibrisgroup.com%3Aprimo3-Article-medline&rft.artnum=&rft.atitle=EASL+2017+Clin

23. Kaneko S, Miller RH, Feinstone SM, Unoura M, Kobayashi K, Hattori N, et al. Detection of serum hepatitis B virus DNA in patients with chronic hepatitis using the polymerase chain reaction assay. Proc Natl Acad Sci U S A [Internet]. 1989 Jan 1 [cited 2018 Nov 8];86(1):312–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2643103

24. Garcia JGN, Ma S-F, Ma S-F. Polymerase chain reaction: A landmark in the history of gene technology. Crit Care Med [Internet]. 2005 Dec [cited 2018 Nov 12];33(Suppl):S429–32. Available from: https://sfx.aub.aau.dk/sfxaub?ctx_enc=info%3Aofi%2Fenc%3AUTF-8&ctx_tim=2018-11-12T14%3A04%3A23IST&ctx_ver=Z39.88-2004&frbrversion=3&req.language=dan&rfr_id=info%3Asid%2Fprimo.exlibrisgroup.com%3Aprimo3-Article-ovid&rft.artnum=&rft.atitle=Polymerase+chain+

25. Bouckaert R, Simons BC, Krarup H, Friesen TM, Osiowy C. Tracing hepatitis B virus (HBV) genotype B5 (formerly B6) evolutionary history in the circumpolar Arctic through phylogeographic modelling. PeerJ [Internet]. 2017 [cited 2018 Sep 20];5(8):e3757. Available from: https://sfx.aub.aau.dk/sfxaub?ctx_enc=info%3Aofi%2Fenc%3AUTF-8&ctx_tim=2018-09-20T17%3A46%3A23IST&ctx_ver=Z39.88-2004&req.language=dan&rfr_id=info%3Asid%2Fprimo.exlibrisgroup.com%3Aprimo3-Article-medline&rft.artnum=&rft.atitle=Tracing+hepatitis+B+virus+(H

26. Norder H, Couroucé A-M, Coursaget P, Echevarria JM, Lee S-D, Mushahwar IK, et al. Genetic diversity of hepatitis B virus strains derived worldwide: genotypes, subgenotypes, and HBsAg subtypes. Intervirology [Internet]. 2004 [cited 2018 Nov 12];47(6):289–309. Available from: https://sfx.aub.aau.dk/sfxaub?ctx_enc=info%3Aofi%2Fenc%3AUTF-8&ctx_tim=2018-11-12T14%3A45%3A49IST&ctx_ver=Z39.88-2004&frbrversion=4&req.language=dan&rfr_id=info%3Asid%2Fprimo.exlibrisgroup.com%3Aprimo3-Article-karger_s&rft.artnum=&rft.atitle=Genetic+Diver

27. Buti M, Rodriguez-Frias F, Jardi R, Esteban R. Hepatitis B virus genome variability and disease progression: the impact of pre-core mutants and HBV genotypes. J Clin Virol [Internet]. 2005 Dec [cited 2018 Nov 12];34:S79–82. Available from:

http://linkinghub.elsevier.com/retrieve/pii/S1386653205800150

28. Schaefer S. Hepatitis B virus: significance of genotypes. J Viral Hepat [Internet]. 2005 Mar [cited 2018 Nov 12];12(2):111–24. Available from: https://sfx.aub.aau.dk/sfxaub?ctx_enc=info%3Aofi%2Fenc%3AUTF-8&ctx_tim=2018-11-12T17%3A00%3A57IST&ctx_ver=Z39.88-2004&frbrversion=4&req.language=dan&rfr_id=info%3Asid%2Fprimo.exlibrisgroup.com%3Aprimo3-Article-wj&rft.artnum=&rft.atitle=Hepatitis+B+virus%3A+significance+of+genotypes&rft.au=Schaefer%2C+S.&rft.aucorp=&rft.auinit=&rft.auinit1=&rft.auinitm=&rft.aulast=Schaefer&rft.ausuffix=&rft.btitle=&rft.coden=&rft.date=2005-03&rft.eisbn=&rft.eissn=1365-2893&rft.epage=124&rft.genre=article&rft.isbn=&rft.issn=1352-0504&rft.issue=2&rft.jtitle=Journal+of+Viral+Hepatitis&rft.object_id=&rft.pages=111-24&rft.part=&rft.quarter=&rft.sici=&rft.spage=111&rft.ssn=&rft.volume=12&rft_dat=%3Cwj%3E10.1111%2Fj.1365-2893.2005.00584.x%3C%2Fwj%3E%3Cgrp_id%3E8138875732055223974%3C%2Fgrp_id%3E%3Coa%3E%3C%2Foa%3E%3Curl%3E%3C%2Furl%3E&rft_id=info%3Adoi%2F10.1111%2Fj.1365-2893.2005.00584.x&rft_id=info%3Aoai%2F%3E&rft_id=info%3Apmid%2F&rft_pqid=17810481&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3A&svc.fulltext=yes&svc.holdings=yes&svc_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Asch_svc&url_ctx_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Actx&url_ver=Z39.88-2004&vid=main

29. Langer BCA, Frösner GG, von Brunn A. Epidemiological study of viral hepatitis types A, B, C, D and E among Inuits in West Greenland. J Viral Hepat. 1997;4(5):339–49.

30. Terrault NA, Bzowej NH, Chang K-M, Hwang JP, Jonas MM, Murad MH, et al. AASLD guidelines for treatment of chronic hepatitis B. Hepatology [Internet]. 2016 Jan [cited 2019 Jan 18];63(1):261–83. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26566064

31. Stevens CE, Beasley RP, Tsui J, Lee W-C. Vertical Transmission of Hepatitis B Antigen in Taiwan. N Engl J Med [Internet]. 1975 Apr 10 [cited 2018 Oct 24];292(15):771–4. Available from: http://www.nejm.org/doi/abs/10.1056/NEJM197504102921503

32. Beasley RP, Hwang L-Y, Lin C-C, Leu M-L, Stevens CE, Szmuness W, et al. Incidence of Hepatitis B Virus Infections in Preschool Children in Taiwan. J Infect Dis [Internet]. 1982 Aug 1 [cited 2018 Oct 24];146(2):198–204. Available from: http://academic.oup.com/jid/article/146/2/198/1037107/Incidence-of-Hepatitis-B-Virus-Infections-in

33. A. T, B.J. M, A. K, G. M, V. C, M.G. B, et al. Viral hepatitis in the Arctic. A review from a Circumpolar Workshop on Viral hepatitis, ICCH13. Alaska Med [Internet]. 2006;49(2 Suppl):193–203. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed7&NEWS=N&AN=17929632

34. Das P, Ahuja A, Gupta S. Overview of the histopathology of chronic hepatitis B infection. Hepat B Annu [Internet]. 2012 [cited 2018 Nov 14];9(1):49. Available from: http://www.hepatitisbannual.org/text.asp?2012/9/1/49/193289

35. Pinter M, Peck-Radosavljevic M. Review article: systemic treatment of hepatocellular carcinoma. Aliment Pharmacol Ther [Internet]. 2018 Sep 1 [cited 2018 Nov 15];48(6):598–609. Available from: http://doi.wiley.com/10.1111/apt.14913

36. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin [Internet]. 2018 Nov 1 [cited 2018 Nov 15];68(6):394–424. Available from: http://doi.wiley.com/10.3322/caac.21492

37. Statistics Greenland. Death causes-viral hepatitis. [Internet]. [cited 2019 Feb 26]. Available from: http://bank.stat.gl/pxweb/en/Greenland/Greenland__SU__SU01/SUXLDA1.px/?rxid=1f04dd0f-1d06-43af-b800-244fc2807e0b

38. Mast EE, Weinbaum CM, Fiore AE, Alter MJ, Bell BP, Finelli L, et al. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) Part II: immunization of adults. MMWR Recomm reports Morb Mortal Wkly report Recomm reports [Internet]. 2006 Dec 8 [cited 2018 Nov 26];55(RR-16):1-33; quiz CE1-4. Available from: https://sfx.aub.aau.dk/sfxaub?ctx_enc=info%3Aofi%2Fenc%3AUTF-8&ctx_tim=2018-11-26T14%3A56%3A40IST&ctx_ver=Z39.88-2004&frbrversion=2&req.language=dan&rfr_id=info%3Asid%2Fprimo.exlibrisgroup.com%3Aprimo3-Article-jstor_archive_10&rft.artnum=&rft.atitle=A+Com

39. Hepatitis B, Acute | 2012 Case Definition. [cited 2018 Nov 15]; Available from: https://wwwn.cdc.gov/nndss/conditions/hepatitis-b-acute/case-definition/2012/

40. Pollicino T, Saitta C. Occult hepatitis B virus and hepatocellular carcinoma. World J Gastroenterol [Internet]. 2014 May 28 [cited 2018 Nov 15];20(20):5951–61. Available from:

http://www.ncbi.nlm.nih.gov/pubmed/24876718

41. Caligiuri P, Cerruti R, Icardi G, Bruzzone B. Overview of hepatitis B virus mutations and their implications in the management of infection. World J Gastroenterol [Internet]. 2016 [cited 2018 Nov 14];22(1):145–54. Available from: https://sfx.aub.aau.dk/sfxaub?ctx_enc=info%3Aofi%2Fenc%3AUTF-8&ctx_tim=2018-11-14T13%3A11%3A15IST&ctx_ver=Z39.88-2004&frbrversion=2&req.language=dan&rfr_id=info%3Asid%2Fprimo.exlibrisgroup.com%3Aprimo3-Article-medline&rft.artnum=&rft.atitle=Overview+of+he

42. Olsen OR, Skinhøj P, Krogsgaard K BL, Olsen OR, Skinhøj P, Krogsgaard K, Baek L. Hepatitis B--an endemic sexually transmitted infection in a local community in Greenland [Internet]. Ugeskrift for laeger Jun 26, 1989 p. 1668–70. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2781630

43. Skinhøj P. Hepatitis B virus infection in children. A sero-epidemiological study in three endemic areas. Trans R Soc Trop Med Hyg [Internet]. 1979 [cited 2018 Oct 25];73(5):549–52. Available from: https://sfx.aub.aau.dk/sfxaub?ctx_enc=info%3Aofi%2Fenc%3AUTF-8&ctx_tim=2018-10-25T17%3A15%3A08IST&ctx_ver=Z39.88-2004&frbrversion=3&req.language=dan&rfr_id=info%3Asid%2Fprimo.exlibrisgroup.com%3Aprimo3-Article-sciversesciencedirect_elsevier&rft.artnum=&rf

44. Skinhøj P. Hepatitis and hepatitis B-antigen in Greenland. II: Occurrence and interrelation of hepatitis B associated surface, Core, and “E” antigen-antibody systems in a highly endemic area. Am J Epidemiol. 1977;

45. Børresen ML, Olsen OR, Ladefoged K, McMahon BJ, Hjuler T, Panum I, et al. Hepatitis D outbreak among children in a hepatitis B hyper-endemic settlement in Greenland. J Viral Hepat. 2010;

46. Niclasen B, Mulvad G. Health care and health care delivery in Greenland. Int J Circumpolar Health. 2012;

47. Greenland in Figures 2018 [Internet]. [cited 2018 Nov 26]. Available from: http://www.stat.gl/dialog/main.asp?lang=en&version=2018&sc=GF&subthemecode=P1&colcode=P

48. Pedersen ML. Diabetes in Greenland 2008-2017 A new model of diabetes care in Greenland based on continued monitoring, analysis and adjustment of initiatives taken. Aarhus University;

2018.

49. Skinhøj P. Hepatitis and hepatitis B-Antigen in Greenland. Am J Epidemiol [Internet]. 1974;71(2):176–85. Available from: http://www.ncbi.nlm.nih.gov/pubmed/3883696

50. Misfeldt JC, Senderovitz F, Melbye M, Olsen J. Sexual behavior and knowledge of AIDS. A study among young people in Greenland. UgeskrLaeger. 1989;

51. Homøe A-S, Berntsen S, Pedersen ML. Gonorrhoea in Greenland: geographic differences in diagnostic activity and incidence of gonorrhoea in 2015. Int J Circumpolar Health [Internet]. 2018 Jan 4 [cited 2019 Feb 11];77(1):1445938. Available from: https://www.tandfonline.com/doi/full/10.1080/22423982.2018.1445938

52. Rokkjaer MS, Jensen MT, Grønbaek H, Jepsen P, Pedersen HS, Vilstrup H. Discharge diagnoses of liver diseases in Nuuk Greenland compared to a Danish county hospital. Int J Circumpolar Health. 2006;65(2):162–8.

53. Lavik B, Holmegaard C, Becker U. Drinking patterns and biochemical signs of alcoholic liver disease in Danish and Greenlandic patients with alcohol addiction. Int J Circumpolar Health [Internet]. 2006;65(3):219–27. Available from: https://www.tandfonline.com/doi/pdf/10.3402/ijch.v65i3.18103

54. Gunnarsdottir SA, Olsson R, Ólafsson S, Cariglia N, Westin J, Thjódleifsson B, et al. Liver cirrhosis in Iceland and Sweden: Incidence, aetiology and outcomes. Scand J Gastroenterol. 2009;44(8):984–93.

55. Dufour MC, Stinson FS, Caces MF. Trends in cirrhosis morbidity and mortality: United States, 1979-1988. Vol. 13, Seminars in Liver Disease. 1993. p. 109–25.

56. Day CP. Heavy drinking greatly increases the risk of cirrhosis in patients with HCV hepatitis. Gut [Internet]. 2001 Dec [cited 2019 Feb 21];49(6):750–1. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11709504

57. Lin CW, Lin CC, Mo LR, Chang CY, Perng DS, Hsu CC, et al. Heavy alcohol consumption increases the incidence of hepatocellular carcinoma in hepatitis B virus-related cirrhosis. J Hepatol [Internet]. 2013 [cited 2019 Feb 21];58(4):730–5. Available from: https://sfx.aub.aau.dk/sfxaub?ctx_enc=info%3Aofi%2Fenc%3AUTF-8&ctx_tim=2019-02-21T15%3A56%3A26IST&ctx_ver=Z39.88-

2004&frbrversion=4&req.language=dan&rfr_id=info%3Asid%2Fprimo.exlibrisgroup.com%3Aprimo3-Article-sciversesciencedirect_elsevier&rft.artnum=&rf

58. Friborg J, Koch A, Wohlfarht J, Storm HH, Melbye M. Cancer in Greenlandic Inuit 1973-1997. Int J Circumpolar Health. 2004;

59. Rex KF, Krarup HB, Laurberg P, Andersen S. Inuit living in Greenland and Greenland Inuit migrated to Denmark have similar high prevalence of markers of viral hepatitis. Int J Circumpolar Health [Internet]. 2013;72:715–7. Available from: http://dx.doi.org/10.3402/ijch.v72i0.22447

60. Bjorn-Mortensen K, Ladefoged K, Obel N, Helleberg M. The HIV epidemic in Greenland - A slow spreading infection among adult heterosexual Greenlanders. Int J Circumpolar Health [Internet]. 2013 Jan 19 [cited 2019 Feb 12];72(1):19558. Available from: https://www.tandfonline.com/doi/full/10.3402/ijch.v72i0.19558

61. Landslægeembedet [Internet]. [cited 2019 Feb 12]. Available from: http://nun.gl/

62. Albertsen N, Fencker IM, Noasen HE, Pedersen ML. Immunisation rates among children in Nuuk. Int J Circumpolar Health [Internet]. 2018 Jan 2 [cited 2018 Nov 26];77(1):1426948. Available from: https://sfx.aub.aau.dk/sfxaub?ctx_enc=info%3Aofi%2Fenc%3AUTF-8&ctx_tim=2018-11-26T15%3A53%3A39IST&ctx_ver=Z39.88-2004&frbrversion=2&req.language=dan&rfr_id=info%3Asid%2Fprimo.exlibrisgroup.com%3Aprimo3-Article-pubmed_central&rft.artnum=&rft.atitle=Immunis

63. Børresen ML, Koch A, Biggar RJ, Ladefoged K, Melbye M, Wohlfahrt J, et al. Effectiveness of the targeted hepatitis B vaccination program in Greenland. Am J Public Health. 2012;

64. Andersen S, Rex KF, Noahsen P, Sørensen HCF, Larsen NH, Mulvad G, et al. Forty-five year trends in overweight and obesity in an indigenous arctic inuit society in transition and spatiotemporal trends. Am J Hum Biol [Internet]. 2014 Jul 1 [cited 2018 Oct 29];26(4):511–7. Available from: http://doi.wiley.com/10.1002/ajhb.22556

65. The Danish Health Data Authority. The Register of Causes of Death [Internet]. Aarhus University; 2018 [cited 2019 Mar 5]. Available from: http://econ.au.dk/the-national-centre-for-register-based-research/danish-registers/the-register-of-causes-of-death/

66. Bojesen L. Patobank [Internet]. [cited 2019 Mar 5]. Available from: http://www.patobank.dk/index.php?ID=21&lang=da

67. Naito H, Hayashi S, Abe K. Rapid and specific genotyping system for hepatitis B virus corresponding to six major genotypes by PCR using type-specific primers. J Clin Microbiol. 2001;

68. Cuhadar S, Koseoglu M, Atay A, Dirican A. The effect of storage time and freeze-thaw cycles on the stability of serum samples. Biochem Medica. 2013;

69. Van Den Besselaar AMHP, Witteveen E, Van Der Meer FJM. Long-term stability of frozen pooled plasmas stored at - 70 C, - 40 C, and - 20 C for prothrombin time and International Normalized Ratio (INR) assessment. Thromb Res. 2013;

70. Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, et al. GRADE guidelines 6. Rating the quality of evidence--imprecision. J Clin Epidemiol [Internet]. 2011 Dec [cited 2018 Jul 27];64(12):1283–93. Available from: https://sfx.aub.aau.dk/sfxaub?ctx_enc=info%3Aofi%2Fenc%3AUTF-8&ctx_tim=2018-07-27T17%3A56%3A20IST&ctx_ver=Z39.88-2004&frbrversion=5&req.language=dan&rfr_id=info%3Asid%2Fprimo.exlibrisgroup.com%3Aprimo3-Article-sciversesciencedirect_elsevier&rft.artnum=&rf

71. Alderson P. Research pointers: Survey of claims of no effect in abstracts of Cochrane reviews. BMJ [Internet]. 2003 Mar 1 [cited 2018 Jul 27];326(7387):475–475. Available from: http://www.bmj.com/cgi/doi/10.1136/bmj.326.7387.475

72. Rex KF, Larsen NH, Rex H, Niclasen B, Pedersen ML. A national study on weight classes among children in Greenland at school entry. Int J Circumpolar Health [Internet]. 2014 Jan 20 [cited 2018 Oct 29];73(1). Available from: https://www.tandfonline.com/doi/full/10.3402/ijch.v73.25537

73. Liver Disease & Hepatitis Program | Alaska Native Tribal Health Consortium [Internet]. [cited 2019 Feb 13]. Available from: https://anthc.org/what-we-do/clinical-and-research-services/hep/

74. SOMUNCU JOHANSEN I, WEIS N, BREHM CHRISTENSEN P, Brehm Christensen P. Viral hepatitis in Denmark. Viral Hepatit Derg [Internet]. 2014 Aug 5 [cited 2019 Feb 13];20(2):43–8. Available from: https://sfx.aub.aau.dk/sfxaub?ctx_enc=info%3Aofi%2Fenc%3AUTF-8&ctx_tim=2019-02-13T13%3A43%3A00IST&ctx_ver=Z39.88-2004&req.language=dan&rfr_id=info%3Asid%2Fprimo.exlibrisgroup.com%3Aprimo3-Article-crossref&rft.artnum=&rft.atitle=Viral+hepatitis+in+Denmark&

75. Stensgaard T, Sørensen T. Telemedicine in Greenland - The creation of an evaluation plan. J Telemed Telecare. 2001;

76. Stensgaard T. Telemedicine in Greenland – from the early beginnings to the making of a business plan. J Telemed Telecare. 2002;

77. Bjerregaard P, Jørgensen T, Lumholt P, Mosgaard L, Borch-Johnsen K, Backer V, et al. Higher blood pressure among Inuit migrants in Denmark than among the Inuit in Greenland. J Epidemiol Community Health. 2002;

78. Prener A, Nielsen NH, Hansen JPH, Jensen OM. Cancer pattern among greenlandic inuit migrants in Denmark, 1968–1982. Br J Cancer. 1987;

79. Boysen T, Friborg J, Andersen A, Poulsen GN, Wohlfahrt J, Melbye M. The Inuit cancer pattern - The influence of migration. Int J Cancer. 2008;122(11):2568–72.

80. Karayiannis P, Karayiannis. Hepatitis D virus. Rev Med Virol [Internet]. 1998 Jan 1 [cited 2019 Feb 12];8(1):13. Available from: https://sfx.aub.aau.dk/sfxaub?2-l=&ctx_enc=info%3Aofi%2Fenc%3AUTF-8&ctx_tim=2019-02-12T18%3A04%3A33IST&ctx_ver=Z39.88-2004&frbrversion=7&req.language=dan&rfr_id=info%3Asid%2Fprimo.exlibrisgroup.com%3Aprimo3-Article-proquest&rft.artnum=&rft.atitle=Hepatiti

81. Cheng HH, Wang DQ, Minuk GY, Anand CM, Stowe TC, Buchan KA. The prevalence of antibody to delta virus in western Canada. Clin Invest Med [Internet]. 1986 [cited 2019 Mar 4];9(3):156–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/3757321

82. Ratnam S, Head CB, Butler RW. Lack of evidence of hepatitis D (delta) infection in Newfoundland and Labrador. Can Med Assoc J [Internet]. 1986;134(8):905–7. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1490973/pdf/cmaj00116-0049.pdf

83. McMahon BJ. Viral hepatitis in the Arctic. Int J Circumpolar Health [Internet]. 2004 Sep 15 [cited 2019 Mar 4];63(sup2):41–8. Available from: https://www.tandfonline.com/doi/full/10.3402/ijch.v63i0.17784

84. C. W, C. L, G.V. M, E. O. Stress, coping, and well-being among the Yup'ik of the Yukon-Kuskokwim Delta: the role of enculturation and acculturation. Int J Circumpolar Health. 2007;

85. Seale JP, Shellenberger S, Spence J. Alcohol problems in Alaska Natives: Lessons from the Inuit. Am Indian Alaska Nativ Ment Heal Res. 2006;13(1):1–31.

86. Wardman D, Quantz D. An exploratory study of binge drinking in the aboriginal population. Am Indian Alaska Nativ Ment Heal Res [Internet]. 2005;12:49–61. Available from: http://www.ucdenver.edu/academics/colleges/PublicHealth/research/centers/CAIANH/journal/Documents/Volume 12/12(1)_Wardman_An_Exploratory_Study_49-61.pdf

87. Kozlov A, Vershubsky G, Kozlova M. Indigenous Peoples of Northern Russia: Anthropology and Health. Int J Circumpolar Health [Internet]. 2007 Dec 21 [cited 2019 Feb 20];66(sup1):1–184. Available from: https://www.tandfonline.com/doi/full/10.1080/22423982.2007.11864603

88. Madsen MH, Grønbæck M, Bjerregaard P, Becker U, The Greenland Population Study TGP. Urbanization, migration and alcohol use in a population of Greenland Inuit. Int J Circumpolar Health [Internet]. 2005 Jul 15 [cited 2019 Feb 20];64(3):234–45. Available from: https://www.tandfonline.com/doi/full/10.3402/ijch.v64i3.17987

89. E. K, S. K, R. K, B. S-M, T. F, A. H, et al. Cultural and gender convergence in adolescent drunkenness: Evidence from 23 European and North American countries [Internet]. Vol. 165, Archives of Pediatrics and Adolescent Medicine. 2011. p. 152–8. Available from: http://archpedi.ama-assn.org/cgi/reprint/165/2/152%5Cnhttp://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed13&NEWS=N&AN=361237161

90. Curtis T, Kvernmo S, Bjerregaard P. Changing living conditions, life style and health. Int J Circumpolar Health [Internet]. 2005 Dec 15 [cited 2019 Feb 22];64(5):442–50. Available from: https://www.tandfonline.com/doi/full/10.3402/ijch.v64i5.18025

91. Moskalewicz J, Simpura J. Alcohol and alcohol policy in eastern European transitions. J Subst Use [Internet]. 2000 Jan 12 [cited 2019 Feb 22];5(1):30–8. Available from: http://www.tandfonline.com/doi/full/10.3109/14659890009053060

92. National Health Interview Surveys 2005 [Sundheds- og Sygelighedsundersøgelsen 2005 & udviklingen siden 1987 - SIF] [Internet]. National Institute of Public Health. 2006 [cited 2019 Feb 24]. p. 307. Available from: https://www.sdu.dk/da/sif/rapporter/2007/sundhed_og_sygelighed_i_danmark_2005_udviklingen_siden_1987

93. Bjerregaard P, Becker U. Validation of survey information on smoking and alcohol consumption against import statistics, Greenland 1993–2010. Int J Circumpolar Health [Internet]. 2013 Jan 31 [cited 2019 Feb 24];72(1):20314. Available from: https://www.tandfonline.com/doi/full/10.3402/ijch.v72i0.20314

94. Statistics Greenland. PRICE TRENDS. [Internet]. [cited 2019 Feb 24]. Available from: http://www.stat.gl/dialog/main.asp?lang=en&sc=SA&subthemecode=o8&colcode=o&version=201013

95. Li G, Smith GS, Baker SP. Drinking behavior in relation to cause of death among US adults. Am J Public Health [Internet]. 1994 Sep [cited 2019 Feb 24];84(9):1402–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8092362

96. Bjerregaard P. Fatal non-intentional injuries in Greenland. Arct Med Res. 1992;

97. Bjerregaard P. Fatal accidents in Greenland. Arctic Med Res. 1990;

98. Bjerregaard P. Alcohol related deaths in Greenland. Arctic Med Res. 1988;

99. Statistics Greenland. Average Personal Income. 2008. [Internet]. [cited 2019 Feb 24]. Available from: http://www.stat.gl/dialog/main.asp?lang=en&version=201013&sc=SA&colcode=t

100. Statistics Greenland. Tobacco and Alcohol. [Internet]. [cited 2019 Feb 24]. Available from: http://www.stat.gl/dialog/topmain.asp?lang=da&subject=Tobak og alkohol&sc=AL

101. Feldman M, Friedman L, Sleisenger M. Sleisenger and Fordtran's gastrointestinal and liver disease: pathophysiology/diagnosis/management, Vol. 2. 7th ed. Feldman M, Friedman LS SM, editor. Philadelphia: Saunders; 2002. 2305 p.

102. Eng MY, Luczak SE, Wall TL. ALDH2, ADH1B, and ADH1C genotypes in Asians: a literature review. Alcohol Res Health. 2007;

103. Bjerregaard P, Mikkelsen SS, Becker U, Hansen T, Tolstrup JS. Genetic variation in alcohol metabolizing enzymes among Inuit and its relation to drinking patterns. Drug Alcohol Depend. 2014;

104. Mendenhall CL. Alcoholic hepatitis. Clin Gastroenterol [Internet]. 1981 May [cited 2019 Feb 23];10(2):417–41. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7018751

105. SHIOMI S, KUROKI T, MINAMITANI S, UEDA T, NISHIGUCHI S, NAKAJIMA S, et al. Effect of drinking on the outcome of cirrhosis in patients with hepatitis B or C. J Gastroenterol Hepatol. 1992;

106. Mota A, Guedes F, Areias J, Pinho L, Cardoso MF. Alcohol consumption among patients with hepatitis B infection in northern Portugal considering gender and hepatitis B virus genotype differences. Alcohol [Internet]. 2010 Mar 1 [cited 2019 Feb 23];44(2):149–56. Available from: https://www.sciencedirect.com/science/article/pii/S0741832909002183

107. Statistics Greenland [Internet]. [cited 2018 Nov 5]. Available from: http://www.stat.gl/dialog/main.asp?lang=da&version=201602&sc=BE&subthemecode=O2&collcode=O

108. Taida T, Arai M, Kanda T, Hige S, Ueno Y, Imazeki F, et al. The prognosis of hepatitis B inactive carriers in Japan: a multicenter prospective study. J Gastroenterol. 2017;52(1):113–22.

109. Wu J-F, Chiu Y-C, Chang K-C, Chen H-L, Ni Y-H, Hsu H-Y, et al. Predictors of hepatitis B e antigen-negative hepatitis in chronic hepatitis B virus-infected patients from childhood to adulthood. Hepatology [Internet]. 2016 Jan [cited 2018 Jul 27];63(1):74–82. Available from: https://sfx.aub.aau.dk/sfxaub?ctx_enc=info%3Aofi%2Fenc%3AUTF-8&ctx_tim=2018-07-27T14%3A51%3A02IST&ctx_ver=Z39.88-2004&frbrversion=6&req.language=dan&rfr_id=info%3Asid%2Fprimo.exlibrisgroup.com%3Aprimo3-Article-wj&rft.artnum=&rft.atitle=Predictors+of+hepat

110. Wu J-F, Chang M-H. Natural history of chronic hepatitis B virus infection from infancy to adult life - the mechanism of inflammation triggering and long-term impacts. J Biomed Sci [Internet]. 2015 Oct 20 [cited 2018 Jul 27];22(1):92. Available from: https://sfx.aub.aau.dk/sfxaub?ctx_enc=info%3Aofi%2Fenc%3AUTF-8&ctx_tim=2018-07-27T12%3A38%3A44IST&ctx_ver=Z39.88-2004&frbrversion=4&req.language=dan&rfr_id=info%3Asid%2Fprimo.exlibrisgroup.com%3Aprimo3-Article-medline&rft.artnum=&rft.atitle=Natural+history+of+chronic+hepatitis+B+virus+infection+from+infancy+to+adult+life+-+the+mechanism+of+inflammation+triggering+and+long-term+impacts.&rft.au=Wu%2C+Jia-Feng&rft.aucorp=&rft.auinit=&rft.auinit1=&rft.auinitm=&rft.aulast=Wu&rft.ausuffix=&rft.btitle=&rft.coden=&rft.date=20151020&rft.eisbn=&rft.eissn=1423-0127&rft.epage=&rft.genre=article&rft.isbn=&rft.issn=&rft.issue=1&rft.jtitle=Journal+of+biomedical+science&rft.object_id=&rft.pages=92&rft.part=&rft.quarter=&rft.sici=&rft.spage=92&rft.ssn=&rft.volume=22&rft_dat=%3Cmedline%3E26487087%3C%2Fmedline%3E%3Cgrp_id%3E

8087673704657717723%3C%2Fgrp_id%3E%3Coa%3E%3C%2Foa%3E%3Curl%3E%3C%2Furl%3E&rft_id=info%3Adoi%2F10.1186%2Fs12929-015-0199-y&rft_id=info%3Aoai%2F%3E&rft_id=info%3Apmid%2F26487087&rft_pqid=&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&svc.fulltext=yes&svc.holdings=yes&svc_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Asch_svc&url_ctx_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Actx&url_ver=Z39.88-2004&vid=main

111. Mowery PD, Dube SR, Thorne SL, Garrett BE, Homa DM, Nez Henderson P. Disparities in Smoking-Related Mortality Among American Indians/Alaska Natives. Am J Prev Med. 2015;49(5):738–44.

112. Chen J De, Yang HI, Iloeje UH, You SL, Lu SN, Wang LY, et al. Carriers of Inactive Hepatitis B Virus Are Still at Risk for Hepatocellular Carcinoma and Liver-Related Death. Gastroenterology [Internet]. 2010 [cited 2019 Feb 11];138(5):1747–1754.e1. Available from: https://sfx.aub.aau.dk/sfxaub?ctx_enc=info%3Aofi%2Fenc%3AUTF-8&ctx_tim=2019-02-11T02%3A30%3A08IST&ctx_ver=Z39.88-2004&frbrversion=4&req.language=dan&rfr_id=info%3Asid%2Fprimo.exlibrisgroup.com%3Aprimo3-Article-sciversesciencedirect_elsevier&rft.artnum=&rf

113. Tohme RA, Bulkow L, Homan CE, Negus S, McMahon BJ. Rates and risk factors for hepatitis B reactivation in a cohort of persons in the inactive phase of chronic hepatitis B-Alaska, 2001-2010. J Clin Virol. 2013;58(2):396–400.

114. Bunyoz KI, Krarup H, Weis N. A danish nationwide questionnaire study of hepatitis B virus screening before immunosuppressive therapy. Dan Med J [Internet]. 2017 Mar 1 [cited 2019 Jan 18];64(3):<xocs:firstpage xmlns:xocs=""/>. Available from: https://sfx.aub.aau.dk/sfxaub?ctx_enc=info%3Aofi%2Fenc%3AUTF-8&ctx_tim=2019-02-13T13%3A53%3A17IST&ctx_ver=Z39.88-2004&frbrversion=2&req.language=dan&rfr_id=info%3Asid%2Fprimo.exlibrisgroup.com%3Aprimo3-Article-proquest&rft.artnum=&rft.atitle=A+Danish+nati

115. Bland JM. An Introduction to Medical Statistics, 3rd edition. Oxford Univ Press. 2000;

116. Pearce N, Checkoway H, Kriebel D. Bias in occupational epidemiology studies. Occup Environ Med [Internet]. 2007 Aug 1 [cited 2019 Feb 1];64(8):562–8. Available from: https://sfx.aub.aau.dk/sfxaub?ctx_enc=info%3Aofi%2Fenc%3AUTF-8&ctx_tim=2019-02-01T18%3A23%3A37IST&ctx_ver=Z39.88-2004&req.language=dan&rfr_id=info%3Asid%2Fprimo.exlibrisgroup.com%3Aprimo3-Article-

bmj_journals&rft.artnum=&rft.atitle=Bias+in+occupational+ep

117. Moltke I, Fumagalli M, Korneliussen TSS, Crawford JEE, Bjerregaard P, Jørgensen MEE, et al. Uncovering the genetic history of the present-day greenlandic population. Am J Hum Genet [Internet]. 2015 Jan [cited 2019 Mar 24];96(1):54–69. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0002929714004789

118. Hønge BL, Jespersen S, Medina C, Té D da S, da Silva ZJ, Lewin S, et al. Hepatitis B and Delta Virus Are Prevalent but Often Subclinical Co-Infections among HIV Infected Patients in Guinea-Bissau, West Africa: A Cross-Sectional Study. Chemin IA, editor. PLoS One [Internet]. 2014 Jun 10 [cited 2019 Feb 24];9(6):e99971. Available from: https://dx.plos.org/10.1371/journal.pone.0099971

119. Jepsen P, Johnsen SP, Gillman MW, Sørensen HT. Interpretation of observational studies [Internet]. Vol. 90, Heart. 2004. p. 956–60. Available from: https://heart.bmj.com/content/90/8/956

120. Stang A. Kenneth J. Rothman: Epidemiology. An introduction. Eur J Epidemiol [Internet]. 2012 Oct 27 [cited 2019 Feb 1];27(10):827–9. Available from: https://sfx.aub.aau.dk/sfxaub?ctx_enc=info%3Aofi%2Fenc%3AUTF-8&ctx_tim=2019-02-01T18%3A42%3A09IST&ctx_ver=Z39.88-2004&frbrversion=3&req.language=dan&rfr_id=info%3Asid%2Fprimo.exlibrisgroup.com%3Aprimo3-Article-proquest&rft.artnum=&rft.atitle=Kenneth+J.+Ro

121. Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, et al. GRADE guidelines 6. Rating the quality of evidence - Imprecision. J Clin Epidemiol. 2011;

122. Lucas RM, McMichael AJ. Association or causation: Evaluating links between “environment and disease.” Bulletin of the World Health Organization. 2005.

123. Medicinpriser.dk [Internet]. [cited 2019 Mar 26]. Available from: https://www.medicinpriser.dk/default.aspx

124. Law DG, Rink E, Mulvad G, Koch A. Sexual health and sexually transmitted infections in the North American Arctic. Emerging Infectious Diseases. 2008.

125. Wang T, Wang M, Duan G, Chen X, He Y. Discrepancy in impact of maternal milk on vertical transmission between Hepatitis B virus and Human cytomegalovirus. Int J Infect Dis [Internet]. 2015 Aug [cited 2018 Nov 19];37(C):1–5. Available from:

https://sfx.aub.aau.dk/sfxaub?ctx_enc=info%3Aofi%2Fenc%3AUTF-8&ctx_tim=2018-11-19T17%3A54%3A23IST&ctx_ver=Z39.88-2004&frbrversion=4&req.language=dan&rfr_id=info%3Asid%2Fprimo.exlibrisgroup.com%3Aprimo3-Article-sciversesciencedirect_elsevier&rft.artnum=&rf

126. Shi Z, Yang Y, Wang H, Ma L, Schreiber A, Li X, et al. Breastfeeding of newborns by mothers carrying hepatitis B virus: a meta-analysis and systematic review. Arch Pediatr Adolesc Med [Internet]. 2011 Sep 1 [cited 2018 Nov 19];165(9):837–46. Available from: https://sfx.aub.aau.dk/sfxaub?+adolescent+medicine=&ctx_enc=info%3Aofi%2Fenc%3AUTF-8&ctx_tim=2018-11-19T17%3A40%3A18IST&ctx_ver=Z39.88-2004&frbrversion=7&req.language=dan&rfr_id=info%3Asid%2Fprimo.exlibrisgroup.com%3Aprimo3-Article-ama&rft.artnum=&rft.ati

127. Bancroft WH, Snitbhan R, Scott RMN, Tingpalapong M, Watson WT, Tanticharoenyos P, et al. Transmission of hepatitis B virus to gibbons by exposure to human saliva containing hepatitis B surface antigen. J Infect Dis. 1977;135(1):79–85.

128. Komatsu H, Inui A, Sogo T, Tateno A, Shimokawa R, Fujisawa T. Tears From Children With Chronic Hepatitis B Virus (HBV) Infection Are Infectious Vehicles of HBV Transmission: Experimental Transmission of HBV by Tears, Using Mice With Chimeric Human Livers. J Infect Dis [Internet]. 2012 Aug 15 [cited 2018 Oct 24];206(4):478–85. Available from: https://academic.oup.com/jid/article-lookup/doi/10.1093/infdis/jis293

129. Scott RM, Snitbhan R, Bancroft WH, Alter HJ, Tingpalapong M. Experimental Transmission of Hepatitis B Virus by Semen and Saliva. J Infect Dis [Internet]. 1980 Jul 1 [cited 2018 Oct 24];142(1):67–71. Available from: https://academic.oup.com/jid/article-lookup/doi/10.1093/infdis/142.1.67

130. Yue Y, Jiang H, Shi L, Li L, Xi B, Yu Y, et al. Mechanism of intrauterine infection of hepatitis B virus. World J Gastroenterol [Internet]. 2004;39(4):224–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15130345

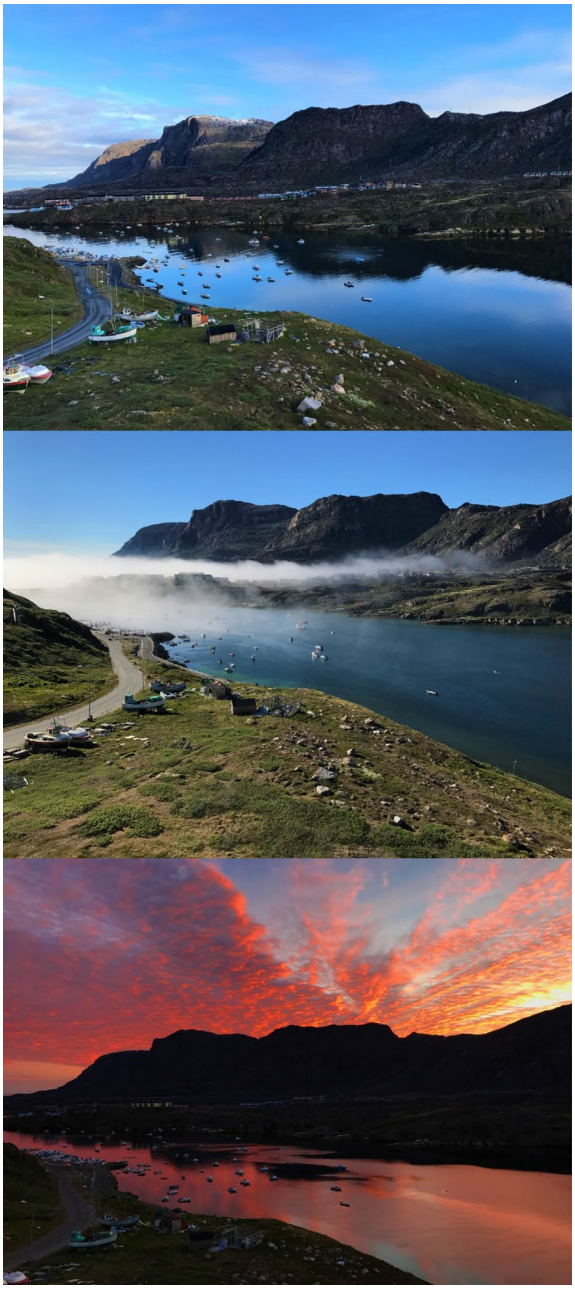
131. Van Der Eijk AA, Niesters HGM, Hansen BE, Pas SD, Richardus JH, Mostert M, et al. Paired, quantitative measurements of hepatitis B virus DNA in saliva, urine and serum of chronic hepatitis B patients. Eur J Gastroenterol Hepatol. 2005;17(11):1173–9.

132. Bond WW, Favero MS, Petersen NJ, Gravelle CR, Ebert JW, Maynard JE. Survival of Hepatitis B Virus After Drying and Storage for One Week. Lancet. 1981;317(8219):550–1.

133. Toshio Shikata, Tsutomu Karasawa, Kenji Abe, Takashi Takahashi, Makoto Mayumi and T. Incomplete Inactivation of Hepatitis B Virus after Heat Treatment at 60 C for 10 Hours Author (s): Toshio Shikata , Tsutomu Karasawa , Kenji Abe , Takashi Takahashi , Makoto Mayumi and Toshitsugu Oda Published by : Oxford University Press Stable URL : h. J Infect Dis. 1978;138(2):242–4.

134. Komatsu H, Sugawara H, Inui A, Nagamine K, Hiejima E, Sogo T, et al. Does the spread of hepatitis B virus genotype A increase the risk of intrafamilial transmission in Japan? J Infect Chemother. 2011;17(2):272–7.

135. Årsberetning 2016 [Internet]. [cited 2019 Feb 19]. Available from: http://nun.gl/-/media/landslaegeembedet/udgivelser/aarsrapport 2016/kap 5/kapitel 5 brnevaccinationer_til_rsberetning_2016_v3_dk.pdf?la=da



Sisimiut, Greenland

APPENDIX

ABSTRACT STUDY 1.

Scandinavian Journal of Gastroenterology. 2012; 47: 692–701

informa
healthcare

ORIGINAL ARTICLE

Population-based comparative epidemiological survey of hepatitis B, D, and C among Inuit migrated to Denmark and in high endemic Greenland

KARSTEN FLEISCHER REX[1,2], HENRIK B KRARUP[3], PETER LAURBERG[4] & STIG ANDERSEN[1,2]

[1]*Department of Internal Medicine, Queen Ingrid's Hospital, Nuuk, Greenland,* [2]*Aalborg University Hospital, Arctic Health Research Centre, Denmark,* [3]*Department of Clinical Biochemistry, Aalborg University Hospital, Denmark, and* [4]*Department of Endocrinology, Aalborg University Hospital, Denmark*

Abstract

Objective. Infection with hepatitis B virus (HBV) is endemic among Arctic populations where it may have a benign course. However, the relation of HBV to migration to low endemic areas is unknown, as it is for hepatitis D and C, and details on the influence of delta virus at a population level are lacking. ***Material and methods.*** Population-based investigation of Greenlanders living in Denmark ($n = 136$) and in Greenland ($n = 441$). We tested for HBsAg, anti-HBs, anti-HBc, HBeAg, anti-HBe, HBV-DNA, HBV genotypes, anti-HDV, HDV-RNA, anti-HCV, HCV-Elisa test, HCV-RNA, aspartate amino-transferase, gamma-glutamyl transferase, bilirubin, and albumin, and performed a physical examination. ***Results.*** Participation rate was 52/95% in Denmark/Greenland. Half of participants in Denmark had lived more than half of their lives in Denmark, and 54.5% had been exposed to HBV. This was similar to 53% among Greenlanders living in West Greenland ($p = 0.76$). HBsAg was positive in 4.4% of Greenlanders in Denmark ($n = 6$), who all were anti-HBe positive and had low viral load. Serological signs of HBV infection associated with having both parents born in Greenland ($p = 0.007$) and with IV drug use ($p = 0.03$). We found serological signs of HDV exposure among participants in Denmark/Greenland in 0.7/1.1% ($n = 1/5$) and HCV exposure in 1.5/0.0% ($n = 2/0$). Liver biochemistry was elevated in Greenlanders exposed to HDV. ***Conclusions.*** Hepatitis B, D, and C occurrences among Greenlanders in Denmark mirrored that of Greenland. Importantly, previously undetected exposure to delta virus associated with elevated liver biochemistry, and the introduction of delta virus is a liability to Greenlanders and to Greenland.

ABSTRACT STUDY 2.

INTERNATIONAL JOURNAL OF CIRCUMPOLAR HEALTH

co-action PUBLISHING

ORIGINAL RESEARCH ARTICLE

Liver biochemistry and associations with alcohol intake, hepatitis B virus infection and Inuit ethnicity: a population-based comparative epidemiological survey in Greenland and Denmark

Karsten Fleischer Rex[1,2]*, Henrik Bygum Krarup[3], Peter Laurberg[2,4] and Stig Andersen[1,2,5]

[1]Department of Internal Medicine, Queen Ingrid's Hospital, Nuuk, Greenland; [2]Arctic Health Research Centre, Department of Clinical Medicine, Aalborg University Hospital, Aalborg, Denmark; [3]Department of Clinical Biochemistry, Aalborg University Hospital, Aalborg, Denmark; [4]Department of Endocrinology, Aalborg University Hospital, Aalborg, Denmark; [5]Department of Geriatric Medicine, Aalborg University Hospital, Aalborg, Denmark

Background. Hepatitis B virus (HBV) infection is common in Arctic populations and high alcohol intake has been associated with an increased risk of a number of diseases. Yet, a description of the influence of alcohol intake in persons with HBV infection on liver biochemistry is lacking.

Objective. We aimed to describe the association between reported alcohol intake and liver biochemistry taking into account also HBV infection, ethnicity, Inuit diet, body mass index (BMI), gender and age in an Arctic population.

Design and methods. Population-based investigation of Inuit (n = 441) and non-Inuit (94) in Greenland and Inuit living in Denmark (n = 136). Participants filled in a questionnaire on alcohol intake and other life style factors. Blood samples were tested for aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), bilirubin, albumin, hepatitis B surface antigen, hepatitis B surface antibody and hepatitis B core antibody. We also performed physical examinations.

Results. Participation rate was 95% in Greenland and 52% in Denmark. An alcohol intake above the recommended level was reported by 12.9% of non-Inuit in Greenland, 9.1% of Inuit in East Greenland, 6.1% of Inuit migrants and 3.4% of Inuit in the capital of Greenland ($p = 0.035$). Alcohol intake was associated with AST ($p < 0.001$) and GGT ($p = 0.001$), and HBV infection was associated with ALP ($p = 0.001$) but not with AST, GGT, bilirubin or albumin in the adjusted analysis. Inuit had higher AST ($p < 0.001$), GGT ($p < 0.001$) and ALP ($p = 0.001$) values than non-Inuit after adjustment for alcohol, diet, BMI and HBV exposure. Ethnic origin modified the association between alcohol and AST, while HBV infection did not modify the associations between alcohol and liver biochemistry.

Conclusions. Non-Inuit in Greenland reported a higher alcohol intake than Inuit. Ethnic origin was more markedly associated with liver biochemistry than was alcohol intake, and Greenlandic ethnicity modified the effect of alcohol intake on AST. HBV infection was slightly associated with ALP but not with other liver biochemistry parameters.

ABSTRACT STUDY 3.

Background Studies in Greenland have suggested a low burden of disease due to chronic hepatitis B virus (HBV) infection.

Objective A 10-year follow-up on all-cause mortality.

Design A cross-sectional population-based clinical study with the addition of a 10-year follow-up based on all electronic medical records.

Setting Greenland.

Participants Adults (n=535) aged 50 through 69 years.

Measurements Baseline data included questionnaires on lifestyle factors, blood samples for liver function tests, hepatitis B serology and virology, and a physical examination. Follow-up was based on information from all available electronic medical records, biopsies, blood samples and radiological descriptions.

Results The participation rate was 95% in the clinical study. The prevalence of chronic HBV infection was 16%. The HBV infection status was not specified in the electronic medical records in the 181 who had died. The crude overall median survival was 70.7 years (95% CI: 69.2-72.0), with a median survival of 67.8 for HBV-infected patients (95% CI: 65.1-69.8) and 71.7 for noninfected patients (95% CI: 69.8-73.4). The risk ratio of infected vs. noninfected patients was 1.7 (95% CI: 1.3-2.2), and the adjusted Cox analysis showed a hazard ratio of 1.6 (95% CI: 1.1-2.3). The adjusted parametric model showed that the predicted median survival time difference was 6.9 years (95% CI: 6.1-7.7), and this survival time was not explained by HBV-related end stage diseases or hepatocellular carcinoma.

Limitations Possible residual confounding.

Conclusions The 10-year follow-up on our cohort did not show HBV-related illnesses or deaths. However, the life span was reduced by 10% in the HBV-infected participants. Hence, HBV infection in Greenland may not be the benign disease that it has been previously suggested to be.

ISSN (online): 2246-1302
ISBN (online): 978-87-7210-471-3

AALBORG UNIVERSITY PRESS